A.M.A.

American Journal of DISEASES OF CHILDREN

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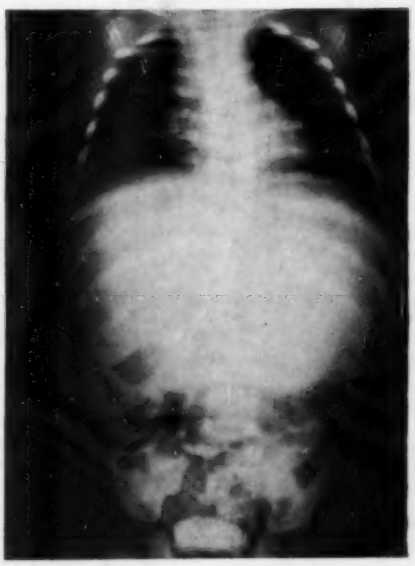

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2. U.S. National Office of Vital Statistics: Vital Statistics of the United States, 1948. Part I. Washington, D.C., U.S. Government Printing Office, 1950.
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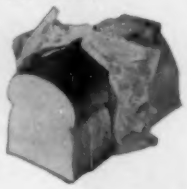

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A.M.A. American Journal OF DISEASES of CHILDREN

Escherichia Coli O127:B_8, a Pathogenic Strain Causing Infantile Diarrhea

I. Epidemiology and Bacteriology of a Prolonged Outbreak in a Premature Nursery

CYRIL S. STULBERG, Ph.D.
WOLF W. ZUELZER, M.D.
ANTHONY C. NOLKE, M.D.
and
ARTHUR L. THOMPSON, M.D., Detroit

A number of distinct serologic types of Escherichia coli have been shown to be responsible for institutional outbreaks as well as sporadic cases of diarrhea in newborn and young infants. In this laboratory an extensive nursery outbreak of diarrhea was studied in 1953 and was shown to be caused by E. coli O111 : B_4.[1] The etiologic role of this organism was evident by its regular presence in virtually pure culture in the stools during the acute stage of the disease and by the simultaneous disappearance of both symptoms and organisms under effective antibiotic therapy. It was observed in the majority of cases that, after therapy was discontinued, the organisms recurred in large numbers in the stools in the absence of renewed diarrheal symptoms, a finding briefly mentioned by others.* Thus, the presence of asymptomatic carriers indicated the pattern of spread of the infection and, as noted also by several investigators,† the large numbers of pathogens excreted seemed to explain the high degree of transmissibility of this disease.

As the result of this experience, periodic checks of the premature nursery were made for the presence of those serotypes of pathogenic E. coli which could be identified with three then-available antisera, namely, O111 : B_4, O55 : B_5, and O26 : B_6. From July, 1953, to December of the same year, none of these serotypes were observed in the nursery, nor was there any clinical diarrhea during this time. During the same period, however, these organisms were repeatedly isolated from sporadic cases of diarrhea admitted to other areas of the hospital.‡

In December, 1953, diarrhea, at times of epidemic proportions, again began to appear in the premature nursery. E. coli, cultured from the affected infants, were not of the

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Read in part before the 55th General Meeting of the Society of American Bacteriologists, New York City, May 8-12, 1955.

From The Child Research Center of Michigan, Children's Hospital of Michigan, and the Departments of Pediatrics and Microbiology, Wayne University College of Medicine.

This investigation was supported in part by a grant from the M. & R. Laboratories, Columbus, Ohio, and, in part by a research grant, P. H. S. E859, from the National Microbiological Institute of the National Institutes of Health, Public Health Service.

* References 2 and 3.

† References 4-6.

‡ Unpublished data.

above-mentioned types. Through the courtesy of Dr. W. W. Ferguson, the organisms were tested at the Michigan Department of Health with antisera then available against four additional serotypes of E. coli associated with infantile diarrhea,[7] O86 : B_7, O119 : B_{14}, O125 : B_{15}, and O126 : B_{16}, but with negative results. Thus the serotypes of E. coli until then observed to be associated with epidemic diarrhea were excluded as etiologic factors. Nevertheless, infants sick with diarrhea were treated on empirical grounds with neomycin, since this drug had proved effective in the earlier epidemic and again seemed to control the symptoms in the individual cases. In the meantime, stool specimens and cultures were saved for future reference.

The diarrhea continued to smolder in the nursery until June, 1954, when it again reached epidemic proportions and a more systematic study was initiated. This report deals with the bacteriologic and epidemiologic aspects and the eventual control of this epidemic which involved a total of 60 cases with 5 fatalities and extended over a period of four months. Although the etiologic agent was eventually established as E. coli O127 : B_8,§ it will be emphasized that the epidemic was recognized as one of E. coli etiology before the actual serotype was identified.

BACTERIOLOGIC METHODS

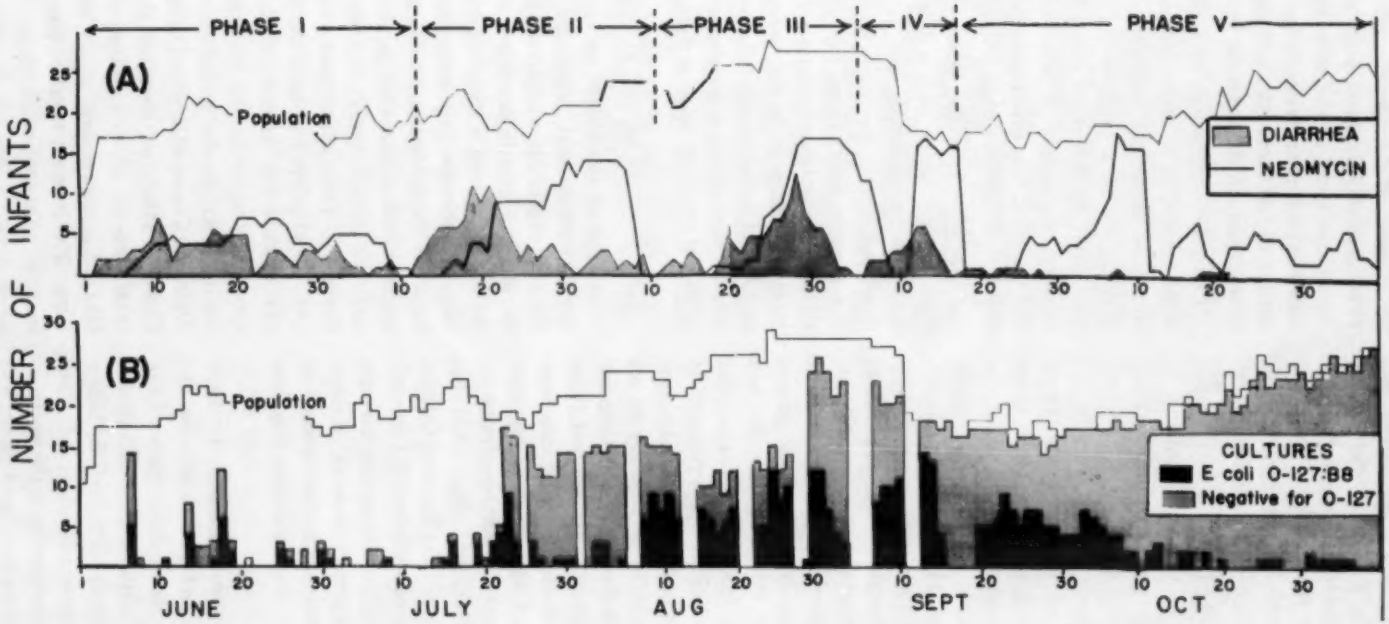
Rectal swabs were plated out on blood agar from which E.-coli-like colonies were picked for immediate serologic typing and for subsequent cultural identification of E. coli. In addition swabs were also cultured on MacConkey's, S. S., and tetrathionate media, in order to exclude the presence of Salmonella or Shigella organisms. On blood agar, the selection of E. coli colonies for typing purposes was facilitated by the fact that in most cases of acute diarrhea, the organisms grew virtually in pure culture. It has been shown that each of the diarrhea-producing strains of E. coli possesses thermostable somatic "O" and thermolabile "B" antigens.[9] Moreover, the diarrhea serotypes identified thus far are distinct from one another in that they do not possess common antigenic groups. In the present study, specific antisera were prepared and titrated according to the methods of Kauffmann.[9] Thus antisera containing "OB" agglutinins were obtained from rabbits immunized with unheated formalinized organisms, and "O" agglutinins from rabbits given heated (100 C for 1½ hr.) organisms, and titers obtained by differential tube agglutination tests[9] were in the order of 1 : 1280 for "OB" sera and 1 : 5120 for "O" sera. When a portion of an individual colony to be typed was mixed with a drop of "OB" antiserum (dil. 1 : 5) on a slide, a positive reaction was immediately apparent by strong, macroscopic agglutination. The "OB" sera were used for rapid screening, while the "O" sera were used to confirm each positive reaction.

In cases where positive reactions to the available antisera were not obtained, stool specimens were stored at —20 C for subsequent study of possible viral agents, and the untyped E. coli isolated from such patients was stocked on nutrient agar for future antigenic analyses. Comparative sensitivities of the predominant E. coli organism from each patient, whether or not it could be serologically typed, were determined against various antibiotics by the disc method on blood agar plates. The results were comparable to those obtained in quantitative sensitivity tests performed through the courtesy of Dr. Myron W. Fisher, of Parke, Davis & Company.

DESCRIPTION OF THE EPIDEMIC

Phase I.—Prior to June 1, 1954, there had been seemingly sporadic cases of diarrhea in the premature nursery which followed no pattern then recognizable to us. On June 1 and 2 there were no cases, but on June 3, two of the seventeen infants then in the nursery had frank diarrhea lasting five and seven days, respectively. On June 6, a third infant, who had had diarrhea during May, had a relapse. At this point stool cultures from 14 infants, including the 3 diarrhea patients, were examined for pathogenic E. coli with the then available antisera. None of the strains tested for (O111 : B_4, O55 : B_5, O26 : B_6) were present. The affected patients received neomycin therapy (100 mg/lb/day) for a period of four to six days and recovered. By June 10, however, five additional cases of diarrhea had occurred, and new infections continued to be observed until the 21st. All the infants with clinical diarrhea were treated with neomycin, but those who were symptom-free did not receive the drug on a prophylactic basis. New admis-

§ References 7 and 8.



Relation of Escherichia coli O127 : B₈ to an epidemic of diarrhea in a premature nursery. *A*, daily incidence of diarrhea and the effect of antibiotic therapy on the course of the epidemic. *B*, incidence of stool cultures positive and negative for E. coli O127 : B₈ in relation to diarrheal disease and treatment.

sions to the nursery continued during this period. As shown in Part *A* of the Figure, by July 6 the nursery was again free of diarrhea and until July 12, only one new case appeared. By this time antibiotic therapy had been discontinued in all infants.

Phase II.—On July 12, the nursery population consisted of 21 premature infants, of whom 8 had recovered from diarrhea. On that and the next day, two of the convalescents had relapses and a recently admitted infant had an increased number of stools. The following day two fresh cases developed, and, as seen in Part *A* of the Figure, the incidence now rose sharply, reaching a peak of 11 cases on July 19. Again the sick infants were treated with neomycin, partly because of the previous experience and partly because the still untyped E. coli isolated from the stools of these infants in virtually pure culture proved to be susceptible to this drug in vitro and their disappearance from the stools seemed to coincide with clinical improvement. It was felt that control of the outbreak by neomycin therapy would point strongly to an E. coli etiology even though at this time the organisms could not be distinguished from ordinary commensal strains. Cultures sent at this time to Dr. Ferguson were reported to be negative for the following strains of E. coli: O111 : B_4, O55 : B_5, O26 : B_6, O86 : B_7, O119 : B_{14}, O125 : B_{15}, and O126 : B_{16}. The incidence of diarrhea did in fact decline sharply. This time neomycin therapy was continued for a period of about 18 days. By Aug. 10 such therapy was discontinued in all cases, and there was again no diarrhea in the nursery.

Phase III.—Almost immediately there were two relapses, and two new cases developed. In the stools of these patients, as well as in other convalescents, an almost simultaneous emergence of E. coli in heavy growth or pure culture was observed. Part *A* of the Figure illustrates how the cycle of relapses and new infections was again repeated. By Aug. 29, sixteen new cases and six relapses had occurred, and on that day 13 of 28 infants were suffering from diarrhea. Again treatment of the affected infants resulted in prompt individual improvement and decline of the outbreak, and again the coliform organisms disappeared from the stools.

Phase IV.—Although by Sept. 5 the outbreak seemed to be under control, there was an almost immediate resurgence of diarrhea, building up to a peak of six cases within nine days. At this point every infant in the nursery, regardless of whether or not he had diarrhea, was given neomycin for a six-day period. The outbreak promptly subsided.

Phase V.—After the fourth cycle of diarrhea was cut short, only a few isolated relapses were observed, but no new cases developed up to the time of this writing, five months later. Upon the appearance of relapses, the entire population of the nursery received neomycin in the period of Oct. 6 to 12, and subsequently all newly admitted infants were given a prophylactic three-day course of the drug upon arrival.

IDENTIFICATION OF THE ETIOLOGIC AGENT

In view of the failure to identify any of the then-recognized pathogenic strains, the E. coli organisms recovered from one of the patients were injected into rabbits in the hope of producing a specific antiserum capable of demonstrating a common etiologic basis for the epidemic. At the same time an antiserum was prepared against a known strain of E. coli O127 : B_8,[8] suplied by Dr. Ferguson. These were ready for use about Oct. 1 and proved to have the same specificity against the known strain as well as specifically agglutinating the organisms from our patients. In the meantime, Dr. W. H. Ewing, Communicable Disease Center, Chamblee, Ga., had identified the organisms from several of our patients as E. coli O127 : B_8, information which reached us on Sept. 20. It now became possible on the basis of cultures and stool specimens saved since June to make a systematic study of this organism in relation to the epidemic and

with a recognizable pathogenic agent to trace, as it were, the epidemiologic pattern back to its beginning.

It will be recalled that some diarrhea had been intermittently noted in the premature nursery since December, 1953. The stool specimens from such cases, dating from this preliminary period, now yielded E. coli O127 : B_8, indicating that the epidemic, in reality, had its beginning at a much earlier time than had been apparent on clinical grounds. For the period referred to as Phase I (June 1-July 12, 1954), stool specimens had been saved more frequently but still not systematically. Part *B* of the Figure shows, however, that E. coli O127 was prevalent in the nursery, and enough data are available to show fairly good correlation between the frequency of the organism in the stools and the incidence of diarrhea as is apparent from a comparison of Parts *B* and *A*. Of 14 stool cultures obtained on June 7, five were positive, indicating that about one-third of the infants were excretors of E. coli O127.

The bacteriologic data for Phase II are reasonably complete after July 23, on which day the entire nursery population was cultured. The incidence of diarrhea was already declining by that time, clearly because the active cases were under treatment with neomycin. On July 23, more than 50% of the infants were excreting E. coli O127. The incidence of positive stool cultures now also decreased rapidly. Continued daily cultures of the stools from the convalescent infants, those with clinical relapses, and the few cases of newly developing diarrhea, when analyzed retroactively, showed virtual disappearance of E. coli O127 while neomycin was being given.

Since at the time of the epidemic itself this information had not been available, the sampling of stools from this group had been continued blindly as it were. It had been noticed at the time, however, that E. coli was reappearing in the stools almost immediately upon the cessation of antibiotic therapy. With the specific antiserum it now became evident that at the beginning of Phase III, between August 10 and 18, at the very time when clinical diarrhea had entirely subsided, 14 asymptomatic infants were intermittently excreting large numbers of E. coli O127. All but one of these infants had had diarrhea previously, the exception being one who subsequently developed the disease. In the next three weeks, five clinical relapses occurred and diarrhea developed in a total of 17 new cases, of which 10 represented recent admissions. In each of these 22 cases, the stools contained practically pure cultures of E. coli O127 during the period of clinical illness. Thus the outbreak of Phase III, which reached its peak on September 29 (Part *A* of Figure), was preceded by the presence of numerous asymptomatic carriers, a few infants in clinical relapse, and infants in the incubation stage of the disease. With antibiotic therapy, the incidence of E. coli O127 declined sharply, paralleling the disappearance of diarrhea almost exactly, as illustrated in the Figure.

The specimens obtained at the beginning of Phase IV, however, showed an almost immediate resurgence of the organisms in the nursery, even though those patients recently placed on neomycin therapy were still receiving the drug. The positive cultures came in part from patients who had been asymptomatic for long periods of time but who had more or less continuously excreted the organism, and partly from newly infected patients who had not yet developed diarrhea. The build-up in positive cultures was indeed rapidly followed by a parallel increase in new diarrhea cases. It was at this point that all the babies in the nursery were given neomycin, and, as seen in Part *A* of the Figure, the incidence of diarrhea now subsided almost completely and never again reached the proportions of a nursery outbreak. Beginning Sept. 16, cultures from every infant then in the nursery subsequently proved negative for four consecutive days.

Phase V is particularly interesting from the bacteriologic and epidemiologic points of view, since it was during this period that the

typing serum for E. coli O127 : B_8 was first used on currently obtained cultures, permitting more accurate and specific control of the infection.

Beginning Sept. 24, every newly admitted infant had been given empirically a three-day course of neomycin for the purpose of preventing the introduction of new pathogenic strains into the nursery. It had been assumed, in view of the previous administration of neomycin to every infant in the nursery for a period of one week and the promptly following disappearance of diarrhea and E. coli from the stools, that the original epidemic had at last been brought under effective control. While there was in fact no further diarrhea, the subsequent bacteriologic analysis (Part *B* of the Figure) shows that this assumption was erroneous. Despite the virtual absence of diarrhea, numerous infants convalescent from previous episodes were still excreting E. coli O127.

The fact that a new outbreak failed to develop during this time may be attributed in part to prophylactic use of neomycin on the newly admitted infants and partly to the use of this drug in a specific manner based on recognition of the organisms by serotyping. Even so, the elimination of the organism from the nursery was not accomplished until all infants had once more been simultaneously placed on therapy for four days and the few cases with persistent excretion were individually controlled with neomycin until discharge. The last positive culture was obtained on Oct. 20 from a patient with bacteriologic but not clinical recurrence.

On Oct. 25, a newborn premature infant was admitted whose stool culture, obtained as part of the admission procedure, was positive for E. coli O127 : B_8. This infant came from the nursery of another hospital at the age of 48 hours and had no clinical evidence of diarrhea. The organisms were present in the stools for three days. This infant, who received neomycin initially and again when another positive stool culture was obtained, never developed diarrhea and eventually had consistently negative cultures and was discharged Nov. 18. In the meantime a second instance of admission of an infant coming into the unit with E. coli O127 in the stools occurred Nov. 1. This infant presented no abnormal symptoms, received neomycin for a period of six days, and excreted no further E. coli O127. There were no cross infections from these two cases. Daily and later biweekly typing of stool cultures of all newly admitted patients, using polyvalent antiserum containing antibody for E. coli O127 : B_8 as well as for seven additional serotypes, has given consistently negative results up to the present time.

COMMENT

The observations presented above conform to the pattern of nursery epidemics of diarrhea caused by pathogenic E. coli strains, such as the E. coli O111 : B_4 outbreak reported from this clinic in 1953 [1] and others.‖ There is ample evidence for the causative role of O127 : B_8 strain isolated from the patients reported here. Although the bacteriologic data for the preliminary period and the early phases of the prolonged outbreak are somewhat incomplete, the general parallelism between clinical manifestations and the presence of E. coli O127 is striking even for that interval. For the later phases the data are complete. Equally significant is the coincidence of clinical improvement with the disappearance of the organisms under the influence of antibiotic therapy. In all individual cases of diarrhea in which testing could be done, either concurrently or retroactively, E. coli O127 was present in large numbers during the acute stage. Conversely, in all but three cases positive stool cultures were associated with clinical diarrhea. Patients in whom only negative cultures were obtained, as, for example, the majority of the infants in Phase V, did not at any time have diarrhea. The three patients with positive cultures in whom diarrhea failed to develop had received neomycin prophylactically just prior to or at the time when the

‖ References 2-6, 8, and 10-13.

cultures were obtained. In keeping with the effect of neomycin in cases of frank diarrhea, it is probable that the use of the drug at such a moment prevented or cut short the development of clinical symptoms and suppressed the growth of the organisms. Then, as in the other patients, bacteriologic relapse without symptoms was observed in these patients.

The incubation period was variable. The blind use of neomycin, suppressing the organisms during the actual epidemic, reduced the number of cases which lent themselves to a determination of the incubation period. However, at the time of these observations the criteria for the early clinical recognition of the disease were not fully developed. These criteria will be more fully discussed in the companion paper.[14] Using birth and admission dates in conjunction with the bacteriologic data, the minimum incubation period could be established as two to three days. On the other hand, periods of from 7 to 14 days elapsed in some instances between the first positive culture and the first recognizable clinical signs of disease. The factors which might influence the duration of the incubation period are not as yet known; variations in the virulence of the infective organisms can reasonably be excluded, since the strain responsible for the outbreak seemed to be uniform as judged by serologic specificity and susceptibility to antibiotics. Nonspecific and specific immunity of the infants, the former possibly related to age, and prematurity might play a part, but these factors remain to be evaluated. It is important in this connection to remember that these patients were premature infants and that somewhat different patterns might be found in full-term newborn or older infants. It is conceivable that the incubation period depends in part on the nature of the preexisting bacterial flora in the intestinal tract of the patients. Since at the time of the manifest disease the pathogenic strain is usually the predominant if not the sole coliform strain present in the intestinal tract, its establishment might be influenced by the type of organisms originally present and the degree to which they are capable of competing with the pathogen. In our patients, the preexisting organism was almost always a nonpathogenic E. coli strain, as might be expected in artificially fed infants. Thus the factors that lead to the conversion of a coliform bacterial flora from one serotype to another should prove interesting for a better understanding of the pathogenesis of the disease. As yet no evidence is available concerning the possible role of phages or inhibiting substances produced by the infecting strain.

The original source of the epidemic could not be established, but it is evident from the the data available that E. coli O127 was present in the unit for a long time before the outbreak was recognized as such. The subsequent finding of E. coli O127 in admission stool specimens of certain of the infants entering the unit without clinical symptoms, at a time when immediate bacteriologic identification and prevention were feasible, shows one way in which pathogenic organisms can enter a nursery. The description of the observed outbreak illustrates how such an organism can spread widely in a short time so that the source may be entirely obscured by the time the epidemic is recognized.

The mode of transmission within the nursery in the face of standard isolation techniques is not clear. The majority of the patients were in Isolettes or incubators, so that airborn droplet infection seems improbable. No special studies were made of fomites, personnel, etc., since at the height of the epidemic the offending organism had not yet been identified. Rogers[10] found E. coli O55 in samples of dust on furniture and in the air during an epidemic caused by that organism, while Jameson and coworkers[6] have shown how nursing personnel may harbor pathogenic E. coli on their hands even after rigorous washing procedures. However, in a previous epidemic due to E. coli O111 in our nursery[1] under conditions almost identical to those of the present epidemic, no organisms were found in air

samples or on floors, cribs, windowsills, etc., or in the personnel. It has been pointed out that the large number of pathogenic organisms excreted from both the patients and the convalescent or incubating carriers is likely to enhance the transmissibility of the infection. It seems to us that the problem involved in the establishment of the abnormal coli flora is likely to be the same as that of the acquisition of the normal bacterial flora in the alimentary tract of the newborn. If the source of ordinary E. coli, or, in the breast-fed infant, of Lactobacillus, were clearly understood, it should greatly clarify the way in which abnormal coliform organisms are transmitted under nursery conditions such as ours.

The significance of the asymptomatic convalescent carriers for the propagation of the epidemic is self-evident. These carriers would seem to account largely for the cyclic outbreaks of diarrhea. Their existence explains why an epidemic of this type could not be permanently controlled as long as only the patients with active diarrhea were subjected to therapy. From the present data and from our previous study,[1] it is clear that with dosages used, neomycin therapy, while successful in sterilizing the stools and thus presumably the large bowel, does not completely eliminate the organisms from the alimentary tract. Therefore a large number of bacteriologic relapses occur which serve as potential sources of new infections within a short time after cessation of therapy. It is not surprising that permanent control of the epidemic was accomplished only after all infants had simultaneously received an effective antibiotic, whether or not they had or had had diarrhea, and after bacteriologic control of the entire unit was established. It will be noted that the majority of the infants with bacteriologic relapse did not at that time show a resurgence of clinical symptoms, though in some instances clinical diarrhea did recur. Whether this diversity in clinical response can be related to the formation of specific antibodies is the subject of a current study to be reported. It is of interest that despite bacteriologic and in some instances clinical relapses, no instance of in vitro resistance to neomycin was observed.

Before discussing the implications of our findings with regard to control and prevention of nursery epidemics caused by pathogenic E. coli strains, it is necessary to stress the special conditions under which the premature nursery of the Children's Hospital of Michigan operates. Unlike ordinary newborn nurseries attached to obstetrical services and receiving clean, newborn infants directly from the delivery room, this nursery must admit infants from a variety of sources, including homes and small hospitals. Moreover, infants are admitted up to several days of age. There is, then, increased opportunity for exposure prior to admission. In spite of unit control by the block system and quarantine, the vagaries of incubation and of clinical manifestations make the introduction of the pathogen a constant threat. This practice affects not only newborn nurseries receiving similar case material but, obviously, infant wards in any hospital accepting patients from the community. Another significant fact in the development of a nursery outbreak would seem to be the length of stay of the individual infant on the unit. In the average obstetric-pediatric nursery, where the stay is a matter of three to five days, the opportunity for the development of an epidemic is limited by the fact that the individual patients leave the hospital so quickly that they may not become infected, or that they show as yet no signs of diarrhea at the time of discharge. Such patients are not infrequently admitted to us subsequently for treatment of diarrhea with positive stool cultures,¶ while the original nursery has no record of any difficulty. In our premature unit, on the other hand, the patients remain for several weeks or longer, and the opportunity for exposure is thus considerably greater.

Regarding control of pathogenic coli infections on infant units of any type, it is evident that adequate bacteriologic diagnosis is a pre-

¶ Unpublished data.

requisite. Rapid identification of the offending organism either by the institutional laboratory or by a centralized service such as a public health laboratory is essential. For the strains thus far shown to be associated with diarrheal disease, polyvalent sera can provide a rapid screening test, which can be followed by exact identification with type-specific serum and bacteriologic analyses. Our experience, however, shows the exigencies arising when an as yet unknown strain is involved, and there is no reason to think that the possibilities are exhausted with the now-established strains. In such situations the preparation of an antiserum against the predominant organisms and the preservation of current stool specimens is essential. At the same time a trial with a suitable antibiotic is clearly indicated but should not be restricted to the obviously affected patients. It is our belief that every patient in the unit should receive prophylactic treatment either until discharge or until bacteriologic identification and control of the organisms has been achieved. Diarrhea due to pathogenic E. coli should be made a reportable communicable disease.

SUMMARY

Bacteriologic, epidemiologic, and clinical data are presented on an extensive nursery epidemic of diarrhea of the newborn caused by a newly described pathogen, E. coli O127 : B_8. The epidemic, which involved a total of 60 cases over a period of four months, was characterized by a cyclic series of flare-ups.

Because stool specimens and daily cultures of the predominant organisms were systematically saved from each infant until the identity of the etiologic agent could be established, it became possible, with a specific antiserum, to make a complete study of the epidemic, using this organism as an etiologic tracer.

The bacteriologic basis for the cyclic pattern of the epidemic then became apparent. Each cycle began with a build-up period during which cross infections and incubation stages were occurring. The incidence of diarrhea increased slowly at first and then rose sharply to a peak. Each sick infant exhibited virtually pure cultures of E. coli O127 : B_8 in its stools. Treatment of the sick infants with neomycin resulted in prompt individual improvement and in a sharp decline of the outbreak, which coincided with the disappearance of E. coli O127 : B_8 from the stools. With the cessation of the antibiotic a new cycle began. There was an almost immediate resurgence of the pathogenic organisms in the stools, resulting invariably in asymptomatic carriers, a few clinical relapses, and an increase in new diarrhea cases.

Control of the epidemic was not accomplished until all infants, whether they had diarrhea or not, were simultaneously placed on neomycin therapy, thus eliminating the organisms from the nursery.

The implications of these findings in the recognition and control of nursery epidemics of infantile diarrhea are discussed.

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The Developmental Evaluation of the Blind Premature Infant

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The developmental evaluation of blind infants is made doubly difficult at the present time,[1] since most of these infants are prematurely born and are blind due to retrolental fibroplasia. We have no specific standards for testing the developmental progress of premature infants with vision, much less those who are blind.

Many times it is important for the parents of blind infants and those who are advising them to have some realistic understanding of the developmental progress of these blind babies. Many blind infants are greatly underestimated as to the possibilities for their development, and other blind infants are not accepted as being mentally retarded, as well as blind.

Gesell * states that his standards for full-term infants are applicable for premature infants if one makes the appropriate correction for the number of weeks of prematurity. He further states that blind children follow the same patterns of neuromuscular and mental development as sighted children, except in visual items.† Griffiths [5] has had the same experience in testing blind infants.

The purpose of this study is to determine whether seemingly normal premature infants can be evaluated by the Gesell norms and, furthermore, whether the same method of evaluation can be applied to blind premature infants.

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* References 2 and 3.

† References 2-4.

MATERIALS AND METHODS

One approach to this problem was to test formally by the Gesell method a sample of blind premature infants, one of premature infants with normal vision, and a control group of full-term infants with normal vision. All infants were tested by the author.

The control group, of full-term infants with normal vision, consisted of 80 infants tested in sequence as part of a routine procedure for an adoption agency. All of these infants received pediatric examinations prior to the developmental examination and were considered normal physically and mentally by the adoption-agency staff. They were all in the homes of the prospective adopting parents and had been in the homes a minimum of three months. Thus adequate time was allowed for an adjustment period.

Among the infants tested for the adoption agency as part of the same routine were 10 additional infants born prematurely, ranging in birth weights from 2 lb. to 5 lb. and 4 oz. These formed the sample of premature infants with vision.

The sample of blind premature infants consisted of 10 premature infants all blind due to retrolental fibroplasia. These infants were referred for this study by the State Services for the Preschool Blind in the Southern California area. Because of the nature of this particular study, infants considered obviously mentally retarded were not referred for testing. The infants tested ranged in birth weight from 2 lb. to 3 lb. and 8 oz. All of these children apparently have complete blindness, except Case 8 and Case 9. The former has some light vision in his right eye and seems to see large objects that are very close to his right eye. However, he has a severe hearing loss in addition to his blindness. Case 9 has some vision in both eyes and can see objects held close to her eyes. The children in this group had all received good care in the homes of their own parents. Of particular significance is the fact that the parents of these infants had all received some help from the educational consultants of the State Services for the Preschool Blind with regard to understanding the development of blind infants and suggestions for giving them satisfactory non-visual sensory experiences.

In the accompanying tables the term Chronological Age refers to the actual age in weeks from the time of birth to the time of examination. The Developmental Age refers to age levels of performance on the Gesell test at the time of examination and is also stated in weeks. The Corrected Age for the premature babies was obtained by subtracting the number of weeks of prematurity from the Chronological Age. The Developmental Quotient was obtained by dividing the Developmental Age by the Chronological Age in the full-term infants and by the Corrected Age in the premature infants and multiplying by 100.

Another more general approach to the problem was to obtain developmental data from questionnaires sent to parents of blind infants. Eight commonly noted developmental items were listed on the questionnaire. The parents were also requested to give the source of the developmental data, namely, memory, baby book, or other written records. In addition, information regarding birth weight and estimated gestational age at the time of birth were requested. These questionnaires were mailed to all parents of blind preschool children registered with the State Services for the Preschool Blind in Southern California. This agency also indicated the cause of blindness as known to them on each questionnaire returned. Only those questionnaires that indicated the source of the data, such as baby books and other written records, the cause of blindness as retrolental fibroplasia, and the birth as premature were accepted for this study.

TABLE 1.—*Summary of All Infants Tested*

	Full Term	Premature	Premature Blind
No. of cases	80	10	10
Average birth weight	?	4 lb. 6 oz.	2 lb. 7 oz.
Average chronological age, wk.	30.3	27.9	41.8
Average wk. of prematurity	0	5.5	10.4
Average corrected age, wk.	30.3	22.4	31.4
Average developmental age	32.4	24.5	32.2
Average developmental quotient = $\frac{\text{dev. age}}{\text{corrected age}}$	106.9	109.3	102.5
Standard deviation of developmental quotients	6.6	8.6	5.4
Developmental quotient range in scores	88-125	96-123	94-116

TABLE 2.—*Normal Premature Infants*

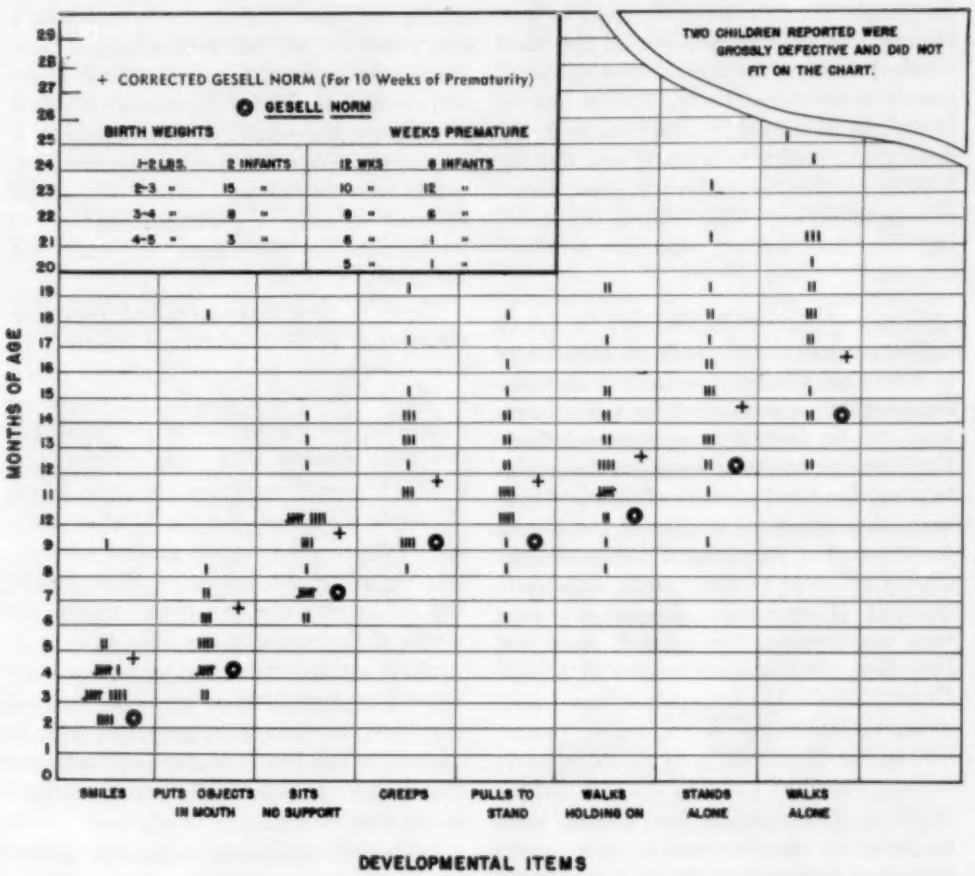
Case	Birth Weight, Lb.-Oz.	Est. Gest., Wk.	Chronological Age, Wk.	Wk. Premature	Corrected Age, Wk.	Development Age, Wk.	Developmental Quotient*
1	2	27	41	13	28	27	96
2	3-9	32	32	8	24	24	100
3	3-15	34	22	6	16	18	112
4	4-6	35	26	5	21	26	123
5	4-11	36	18	4	14	15	107
6	4-15	36	20	4	16	16	100
7	5	36	33	4	29	33	113
8	5	36	28	4	24	26	108
9	5-2	36	33	4	29	32	110
10	5-4	37	26	3	23	28	121
Average	4-6	34.5	27.9	5.5	22.4	24.5	109.3

* Standard deviation of the Developmental Quotient = 8.6.

TABLE 3.—*Blind Premature Infants*

Case	Birth Weight, Lb.-Oz.	Est. Gest., Wk.	Chronological Age, Wk.	Wk. Premature	Corrected Age, Wk.	Development Age, Wk.	Developmental Quotient*
1	2	28	27	12	15	15	100
2	2-3	28	39.5	12	27.5	32	116
3	2-3	30	58	10	48	44	102
4	2-7	32	47	8	39	37	94
5	2-10	29	53	11	42	42	100
6	2-12	32	41	8	33	34	103
7	2-15	27	43	13	30	32	106
8	3-3	28	47	12	35	35	100
9	3-6	31	42.5	9	33.5	35	104
10	3-8	31	25	9	16	16	100
Average	2-7	29.6	41.8	10.4	31.4	32.2	102.5

* Standard deviation of the Developmental Quotient = 5.4.



RESULTS

The results of the groups formally tested by the Gesell tests are indicated in Table 1. The mean developmental quotient of the 80 full-term normal infants was 106.9, that of the normal premature infants 109.3, and that of the blind premature infants 102.5. Thus in all instances they were well within the normal range. The standard deviation of the full-term infant was 6.6, in the normal premature group 8.6, and in the blind premature group 5.4. The difference between the means of these groups was not considered significant, since P—0.05 or greater in each instance. The individual scores of the normal premature infants are recorded in Table 2 and of the blind premature infants in Table 3.

Only 89 of the 250 questionnaires mailed were returned. Of these 89, only 28 indicated that the source of their developmental data was a written record and that the baby was prematurely born and blind due to retrolental fibroplasia. The information from these 28 questionnaires is tabulated in the Chart. It can be seen that the general trend of development for these commonly noted developmental items is the same for prematurely born infants who are blind as for full-term infants with vision.

The median birth weight of these infants is 2 to 3 lb., and the median number of weeks of prematurity is 10 weeks. When we correct the Gesell norms for these 10 weeks of prematurity we find the behavior of the blind infants following the normal developmental pattern even more closely. This is particularly true of smiling, putting objects in the mouth, and pulling to a stand and walking holding on. Sitting without support seems to be generally somewhat delayed, and standing alone and walking alone are definitely delayed.

COMMENT

The purpose of this study, as stated, was to determine whether standards of developmental progress established for full-term infants can be applied to premature infants. Furthermore, can these same standards also be applied to blind premature infants? There have been numerous studies of the mental development of premature infants most adequately reviewed by Alm.[6] Some of the early studies ‡ of premature development were very discouraging, but others § were not. However, the long-term studies of Hess,[11] Blegen,[12] and Alm [6] would indicate quite strongly that, in general, as adults, premature infants do as well in society as full-term infants. This does not deny the fact that the incidence of neurological disorders and mental deficiency may be more frequent among premature infants than among full-term infants but suggests that prematurity alone is not the cause.

From reviewing 49 studies of the mental development of premature infants, Alm [6] concludes that during infancy and the preschool years premature infants are retarded by comparison with full-term children. Gesell [2] and Mohr and Bartelme,[10] however, point out that by giving the infant credit for the number of weeks he is premature, he compares very favorably with full-term infants. In this study we subtracted the number of weeks of prematurity from the weeks of chronological age from birth to arrive at the babies' proper corrected age. The same correction could be obtained by adding the weeks of gestation to each baby's age, premature and full-term alike, and comparing developmental scores. There is always some error in that the number of weeks of gestation is generally an approximation in premature infants. The same error, however, occurs with the full-term infants who are all assumed to have a gestational age of 40 weeks, and no corrections are made for variations.

There is very little published regarding the testing of blind infants or children. In a comprehensive book on blindness edited by Zahl,[13] there is a chapter by Hayes on measuring the intelligence of the blind, but this deals entirely with older children and adults. Elonen [14] reports a complete dearth of standardized tests for the blind at early age levels. Gesell ‖ reports general information regarding the testing of blind infants and reports one case.[4] Griffiths [5] reports the results of the testing of one blind baby at 23 weeks of age and states that only a few blind babies have been tested so far by her method. However, there are many people working in this area at this time, and there will undoubtedly be more published information available in the near future.

In the developmental evaluation of the blind infants obvious allowances were necessary for items that exclusively involve vision, such as regarding the pellet or following the dangling ring with the eyes. However, many items that would seem to be very dependent on eye-hand control were possible through localization of the toy, such as the block, by sound. Once located and grasped, the toys were as deftly explored and manipulated by the blind infants as by sighted infants. A complete analysis of the test items will be reported in a later study. However, certain facts were immediately apparent during this study. On the Gesell scoring forms the items at ages 28, 32, and 36 weeks seem to be

‡ References 7 and 8.

§ References 9 and 10.

‖ References 2-4.

least influenced by blindness, except for sitting without support. Prior to 28 weeks, arm control is poor and many of the adaptive items are related to visual recognition or pursuit. By 40 weeks, fine motor movements begin to dominate, requiring more precise eye-hand control, and after 1 year of age many items related to recognition of pictures, formboard manipulation, and color forms begin to appear.

In general, sitting without support and walking alone were delayed, but pulling to a stand and walking with support were not significantly delayed. This is best illustrated in the response to the questionnaires, in the chart.

It has been stated that the causes of blindness in full-term infants are commonly related to other neurological problems. This would not seem to be the case with blindness due to retrolental fibroplasia, despite the fact that there have been some reports [15] to this effect. This study does not include enough cases to conclude anything regarding the frequency of normal development among infants blind due to retrolental fibroplasia. It does suggest that some of these infants may develop along the usual developmental patterns during infancy. It must be recognized that there were several factors operating in favor of the blind infant in this study, namely, intentional avoidance of cases considered obviously retarded and the guidance given the parents of these children to help them develop normally. The whole purpose of this guidance service is to help the parent understand the developmental possibilities of these blind babies and prevent unintentional functional retardation of the blind baby. It is hoped that with developmental evaluations of this type, such services to blind infants may be strengethened.

SUMMARY

Observations are presented on the developmental testing by the Gesell test of 10 premature infants blind due to retrolental fibroplasia, with 10 premature infants with normal vision and 80 full-term infants serving as controls. The mean corrected developmental quotients of these groups are all well within the normal range. This suggests that when proper correction is made for the weeks of prematurity, the developmental standards for full-term infants can be used in testing premature infants, and this holds true for blind premature infants as well.

The responses of the parents of 28 infants blind due to retrolental fibroplasia to a questionnaire regarding eight developmental items that they had written records of are recorded. Two of the infants are grossly retarded and are off the scale, and the remainder follow the usual developmental pattern of full-term infants, especially when the weeks of prematurity are taken into consideration. Sitting without support, standing alone, and walking alone are definitely delayed, seemingly because of our dependence on vision for balance, whereas smiling, putting objects in the mouth, pulling to a stand, and walking holding on followed more closely the established norms.

The staff of the State Services for the Preschool Blind in the Southern California area, especially Miss Claire Jackson, and the staff of the Holy Family Adoption Service helped in this study.

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Ulcerative Colitis in Children

Observations in Selected Patients

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INTRODUCTION

Ulcerative colitis is not rare in children. Bargen and Kennedy [1] recently reviewed 139 patients observed during a period of 10 years. Smaller groups of cases have been described by others* During the 18 years 1936 to 1954, eighty instances of ulcerative colitis in children have been observed at the University of Chicago. The purpose of this report is to describe four selected patients, illustrating important diagnostic and therapeutic aspects of this complex illness.

CASE 1.—N. M., a 14-year-old white girl student, first experienced mild diarrhea while vacationing in Florida in January, 1953. On returning to Chicago, her bowel movements became numerous and bloody. Although Endamoeba histolytica never was identified, she was treated elsewhere with emetine and later oxytetracycline (Terramycin). After initial improvement, the symptoms recurred, but responded to bed rest and a bland diet. Roentgen examination elsewhere, in November, 1953, indicated minimal changes in the right colon and the adjacent portion of the transverse colon, compatible with ulcerative colitis. In January, 1954, she experienced a sudden profuse hemorrhage from the rectum. Three weeks later a perineal abscess resulted in a small rectovaginal fistula. She lost 12 kg. in weight, developed increasing abdominal cramps, and had several episodes of erythema nodosum.

The patient was first seen by us on March 1, 1954. Physical examination revealed an emaciated, chronically ill girl who was apprehensive but cooperative. There was moderate tenderness in the lower abdomen. The perineum had a purplish inflamed appearance; four prominent hemorrhoidal tags were noted. Immediately distal to the hymenal ring, a small 3-mm.-in-diameter, fistulous opening was identified from which exuded droplets of mucopurulent material. Proctoscopic examination revealed a normal mucosa to 10 cm. above the anus. The patient was afebrile during the entire hospital course. Laboratory studies indicated a hemoglobin of 11.3 gm. per 100 cc., red cell count of 4,200,000 per cubic millimeter, and leucocyte count of 11,000. The feces were positive for occult blood; gross blood was noted prior to therapy. No parasites were identified in the feces; bacteriologic studies revealed the usual flora. Although the colon was not examined roentgenologically at this time, the earlier x-ray findings, together with the clinical evidence, supported the diagnosis of chronic ulcerative colitis.

Therapy consisted of sulfaguanidine, phenobarbital, and belladonna and a low-residue, nonlaxative diet. A penicillin-streptomycin combination was prescribed to decrease the infection in the fistulous tract. Forty units of aqueous corticotropin was administered every eight hours. The appetite became voracious; 5000 calories was consumed daily, and the patient's weight increased from 41 kg. to 51 kg. in two months. The dose of corticotropin (ACTH) was reduced gradually to 30 units per day but later was increased to 80 units daily on discharge from the hospital, because of increased amounts of blood in the stools. With the improvement in bowel function, the discharge from the fistula decreased markedly, providing the patient with a tremendous psychological stimulus. She was discharged from the hospital considerably improved.

Subsequently, on therapy with hydrocortisone, she gained an additional 2.6 kg. Administration of 2.5 mg. of methscopolamine (Pamine) twice daily relieved the abdominal cramps developing after a more liberal diet and increased activity. Within the past several months the patient received 20 mg. of

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* References 2-4.

prednisone (Meticorten),† daily to avoid the rounding of the face induced by Compound F. However, symptoms were not controlled satisfactorily and 40 to 60 mg. of hydrocortisone daily has been resumed. The fistulous channel remains open and drains slightly. The number of bowel movements approximates one daily, but the consistency has varied from mushy to watery. The clinical course recently has been complicated also by two episodes of painful erythema nodosum. Roentgen examination in June, 1955, demonstrated conclusive evidence of ulcerative colitis, involving the ascending and transverse portions of the colon, with loss of normal haustrations, moderate contraction of the bowel, and a pseudopolypoid mucosal pattern (Fig. 1). Despite the recent difficulties, the patient seems to have made satisfactory progress. She has been able to complete an active freshman year at high school, and her general health has improved considerably.

Fig. 1 (Case 1).—Roentgen appearance of colon in June, 1955.

Comment.—The diagnosis of ulcerative colitis usually is established readily on the basis of characteristic changes in the appearance of the rectal mucosa at proctoscopy. However, in approximately 5% of cases with involvement of the colon above the rectum and sigmoid the proctoscopic findings are minimal or nil. The diagnosis then depends upon a suggestive clinical history, the absence of specific pathogenic bacteria or parasites in the feces, and the roentgen appearance of the colon and rectum. In this case, proctoscopy was of secondary importance, whereas the x-rays provided definitive, though initially minimal, evidence of the disease.

The routine use of the tetracycline antibiotics in bloody diarrhea of unknown etiology is undesirable, as this case illustrates. Another noteworthy observation is the temporary healing of the fistula despite the use of corticotropin. We have observed the complete healing of fistulo in ano, rectovaginal fistula, and rectal ulcers during the administration of large doses of corticotropin, cortisone, and hydrocortisone. Despite the currently favorable course, the patient remains susceptible to recurrences of the disease. Careful medical management will be required indefinitely, though the present response and the absence of significant progression of the disease are encouraging.

Case 2.—M. R., a 10-year-old schoolboy, had experienced the onset of ulcerative colitis in the fall of 1947, with occasional streaking of blood on well-formed stools. Proctoscopy at that time reportedly was normal. By 1949 the rectal bleeding had increased, and the patient was given an unspecified sulfonamide with no beneficial effects. Early in 1950, diarrhea developed, with 12 or more

† Prednisone, formerly known by the generic name metacortandracin.

mucoid, bloody, liquid stools daily and a temperature to 40.5 C (104.9 F). "Pinpoint ulcerations" were observed on proctoscopic examination. Hospitalization and treatment with blood transfusions, numerous sulfonamides, chlortetracycline, chloramphenicol, penicillin, and succinylsulfathiazole (Sulfasuxidine) seemed to be effective, and after several weeks the acute illness subsided. In June, 1951, at the age of 6½ years, another recurrence subsided after five weeks of treatment with succinylsulfathiazole, a low-residue diet, and codeine. One month later an exacerbation failed to respond to the usual sulfonamides except salicylazosulfapyridine (Azulfidine); and this drug was continued for three months. However, a subsequent recurrence of bleeding failed to respond to salicylazosulfapyridine, and the boy was brought to us in March, 1953.

The patient was an exceedingly intelligent youngster, alert, and restless. Proctoscopic examination revealed a normal mucosa to 20 cm.; beyond this level there were a few small ulcerations and increased friability of the mucosa. Roentgenologic examination disclosed minimal changes in the transverse colon, splenic flexure, and upper descending colon. A regimen of moderate rest, bland diet, phenobarbital, belladonna, and salicylazosulfapyridine (Azopyrine) was initiated. The patient gained 3 kg. in weight, went to school, but otherwise restricted his activities. On the evening of Jan. 15, 1954, he received a spanking from his parents. The next day he passed eight bloody bowel movements and noted severe abdominal pain, gradually subsiding as the bleeding increased. Proctoscopy on Jan. 21 revealed large amounts of bloody mucus in the rectum; the mucosa was edematous, granular, and slightly friable. The changes, although not severe, had not been present nine months earlier. The patient was admitted to the hospital the same day. The physical and laboratory examinations were normal, except for a temperature of 38.0 C (100.4 F). Numerous examinations were negative for ova and parasites; Pseudomonas aeruginosa was cultured once.

Treatment with rest, diet, sulfaguanidine, phenobarbital, belladonna, and hydrocortisone was ineffective. The stools were mushy; they contained considerable amounts of blood and mucus, and averaged five per day. The proctoscopic changes persisted. On Feb. 26, corticotropin therapy was started; 90 units of aqueous corticotropin daily for two days, 60 units daily for four days, 40 units daily for seven days, and then a gradual decrease to 10 units per day for the next two weeks. The changes within 48 hours were indeed dramatic. The stools became formed and the bleeding decreased greatly. The appearance of the rectal mucosa also improved rapidly. In a 22-day period the ulcerations and bloody discharge disappeared entirely. The patient gained 2.4 kg. The improvement was maintained after corticotropin was discontinued. The patient was discharged on April 3, 1954, having one brown, well-formed stool daily, without occult blood.

The patient has returned to the Clinic regularly, the last visit in June, 1955. His weight has increased, and he has grown an inch in height. The stools continue to be well formed and infrequent; gross blood is not visible. The hemoglobin is normal. At present, therapy includes 2.0 gm. of sulfaguanidine, phenobarbital and belladonna tablets, vitamins, and a liberal bland diet. The patient is an "A" student in school without effort. Every Saturday last summer this 10-year-old boy played nine holes of golf with his father and often carded the low score. There have been no more spankings, at least no physical ones. Evidence of increasing emotional difficulty between the patient and his mother recently led to serious consideration of formal psychotherapy as an additional therapeutic measure. However, family tensions again have subsided, at least for the present, and the boy is living a relatively unrestricted and normal life.

Comment.—This case also illustrates the difficulty in recognition of ulcerative colitis in children. The rectal bleeding, in the absence of obvious proctoscopic changes, is attributed to hemorrhoids or anal fissures. The number of bowel movements and their consistency may be entirely normal, when the process is limited to the rectal mucosa, the only abnormality consisting in the passage of bright red blood in the feces. The roentgen examination of the colon may be normal early in the course of the disease. The fever is ascribed erroneously to a variety of causes. Repeated careful studies are necessary, under such circumstances, to establish the correct diagnosis.

The striking response to one sulfonamide compound, salicylazosulfapyridine in this case, and the lack of improvement with other sulfonamide derivatives and other preparations has been noted many times. Not infrequently, the initial favorable response is only temporary and is not reproducible in subsequent relapses; thus, in this patient the beneficial clinical effect of salicylazosulfapyridine was temporary, and the drug was replaced by sulfaguanidine.

The abrupt exacerbation within hours after emotional stress (a spanking) emphasizes the importance of psychogenic disturb-

ances, if not as a primary, then as a contributory factor. The rectal mucosa is as fragile as the temperament and may reflect or respond to the emotional disorder in a dramatic manner. The role of the parents in the evolution and maintenance of the emotional problems in this boy has not been defined clearly. There is information implicating the dominant, aggressive, and demanding mother as the disturbing factor. The father, at least superficially, appears to be a passive, pliable, and pleasant individual. An important objective of therapy has been the orientation of the mother to a less rigid and obsessive attitude. She cannot be induced to take lightly the illness of her only son, but she has been persuaded to permit the patient and the physician to assume more of the management of the case.

CASE 3.—H. G., an 11½-year-old white girl, was admitted initially on Aug. 31, 1951. She had experienced a brief episode of diarrhea with mild bleeding during the spring of 1946 and had received chlortetracycline (Aureomycin) and chloramphenicol (Chloromycetin), with gradual diminution of symptoms for two months. She then developed severe abdominal cramps, bloody diarrhea, and acute arthritis of various joints. The migratory polyarthritis was treated with corticotropin and cortisone, with improvement. Subsequently, there were many exacerbations of the disease requiring numerous hospitalizations. During acute phases, 6 to 12 bright red or tarry stools were passed daily, particularly when the patient was emotionally disturbed. During remissions the number of bowel movements occasionally would decrease to one daily. Cramping abdominal pain was a major problem and was treated elsewhere by frequent doses of meperidine (Demerol), many sedatives, and deodorized opium tincture. Four different barbiturates and triple-bromide tablets were found in the patient's valise on admission to the hospital; large additional quantities of sedatives, unreported by the patient, were found later in her room. Severe rectal hemorrhages and a persistent hypochromic anemia necessitated frequent blood transfusions. During the four and one-half years of illness, the patient had received more than 300 transfusions of blood. The family history was not unusual. However, the mother was described as highly nervous, the father was away from home most of each week, and the family environment apparently was punctuated by "family squabbles."

Physical examination revealed a thin, pale, and apprehensive child, complaining of abdominal pain, clutching a pillow to her abdomen, and walking in a stooped manner. There was generalized but inconstant tenderness in the abdomen; bowel sounds were increased. There was no evidence of acute arthritis. Proctoscopic examination to a level of 10 cm. above the anal ring revealed a finely granular, nonfriable mucosa, compatible with a healing mild ulcerative colitis.

The hemoglobin fluctuated between 10.0 and 14.5 gm. per 100 cc. and the red cell count between 3,000,000 and 4,800,000 per cubic millimeter. The leucocyte count was 13,250 and the sedimentation rate 36 mm. The feces either contained gross blood

Fig. 2 (Case 3).—Roentgen appearance of colon in 1951.

or were strongly positive for occult blood. Many examinations for ova and parasites were negative; no pathogens were identified on bacteriological study. The serum electrolytes and proteins were normal. X-rays of various joints were normal. Roentgenologic examination of the colon disclosed a loss of haustral pattern, rigidity of the walls, and shortening of the entire colon (Fig. 2).

The hospital course was characterized by very gradual improvement during treatment with 30 mg. of phenobarbital and 7.5 mg. of belladonna extract every eight hours; 1 gm. of succinylsulfathiazole four times daily, and 100 mg. of chloramphenical every six hours. Cortisone was admin-

istered in a total dosage of 840 mg. in 25 days. The patient then improved more rapidly, and the stools decreased to one daily.

Many hours were spent in discussions with the patient. She was an intelligent but introspective and disturbed child. She concealed numerous medications about her bed, played favorites with the nurses and doctors, and behaved in an unpredictable and frustrating manner. As the weeks passed, the complexity and seriousness of her psychiatric difficulties became increasingly obvious. After trial and error, the casual, friendly, yet firm attitude was found most effective in dealing with her changing moods. A psychiatric consultant diagnosed a

Fig. 3 (Case 3).—Roentgen appearance of left colon in 1953.

serious behavior problem and suggested that long-term supportive psychotherapy might be beneficial. Later events brought to light a fundamental problem, characterized by an apparent absence of deep love on the part of the parents for the child and by their inability to deal adequately with her. The father traveled much of the time; the mother, though superficially attentive, was unable emotionally to cope with the patient.

The patient improved so that discharge in mid-October was planned. The date seemed acceptable to the patient, but within 24 hours she demanded in typical fashion an earlier discharge; when this was refused, she exploded into a violently hostile attitude toward the hospital and its staff. Later, it was learned that she frequently expressed her hatred by writing extremely vituperative letters which were not mailed. At discharge, on Oct. 30, 1951, the stools were negative for blood. A regimen of rest, a bland low-residue diet, and phenobarbital, belladonna, and vitamins was prescribed.

Symptoms recurred a few weeks later. In the subsequent one and one-half years she was hospitalized and transfused three times for massive rectal bleeding. Excitement and emotional stress often resulted in bloody diarrhea of several days duration. As before, she consumed large quantities of barbiturate, chloral hydrate, and codeine.

The patient was 13 years old on her second admission, Feb. 8, 1953. She was pale and appeared chronically ill. The abdomen was diffusely tender. Numerous scars on the ankles and thighs indicated the sites of venous cut-downs for previous blood transfusions. The anemia was more pronounced, with a hemoglobin of 9 gm. per 100 cc. and a red blood cell count of 3,200,000. The feces were strongly positive for occult blood. At proctoscopy the rectal mucosa appeared finely granular and bled easily when wiped with a cotton swab. X-rays revealed ulcerative colitis of the entire colon with pseudopolyposis (Fig. 3).

The therapeutic problem had become exceedingly difficult. The patient evinced a definite contempt for authority and disbelief in the medical and nursing staffs. The duet of crying followed by numerous explosive diarrheal stools was a daily sequence in spite of sedation and extreme benevolence on the part of the attending staff. The patient, on the average, passed eight liquid stools per day. Therapy included sulfaguanidine, phenobarbital, belladonna, vitamins, and a low-residue, nonlaxative diet. After the first two months the patient gained 3 kg. The hemoglobin had risen to 12.1 gm/100 cc. (additional blood had not been administered). The two daily bowel movements were well formed, although consistently positive for occult blood. The first menstrual period, associated with only moderate pain, occurred on March 30, 1953.

Psychiatric interviews were held three times each week. During the course of these visits the patient had had occasion to see, through the locked door, the closed psychiatric unit of the hospital. Later (April, 1953) she heard or thought she heard discussions of her removal to this unit, where the most disturbed patients were quartered. Her anxiety increased rapidly to acute agitation and panic. The following day a severe rectal hemorrhage occurred, and the blood pressure fell to 70 mm. of Hg systolic and 0 diastolic. Blood was administered, but after 100 cc. the patient had another reaction, again responding to epinephrine and diphenhydramine (Benadryl). A fresh unit of 500 cc. of blood then was given without incident. The systolic pressure rose to 104 mm. of Hg and

the diastolic to 60 mm. The hemoglobin, 12 gm. prior to the bleeding, was only 8.6 gm. per 100 cc., in spite of the transfusion.

Twenty-five milligrams of cortisone was administered orally every six hours the same day. For the next 48 hours there were no bowel movements or further rectal bleeding. The patient tolerated a pint of blood daily for two days. On therapy with cortisone (725 gm. in 17 days), the stools became brown in color and less watery. The hemoglobin rose to 12.0 gm. per 100 cc. A deep necrotic ulcer developed at the site of an old venous cutdown; debridement was necessary, and healing was slow. Soon afterward the patient again complained of pain in various joints; there was no demonstrable swelling or heat; however, the temperature frequently rose to 39.4 C (102.92 F). The symptoms finally subsided after a month of therapy with salicylates. On Sept. 15, another massive hemorrhage from the rectum resulted in shock. Four pints of blood was necessary to maintain the blood pressure and hemoglobin at acceptable levels.

The patient's need for skillful psychotherapy had become increasingly urgent. In October, 1953, a competent young woman psychiatrist was induced to enter the situation as an active therapist. The patient rapidly developed excellent rapport with her; the beneficial influence upon the young girl's thinking, reactions to emotional situations, and orientation to other children, to the doctors, and to the hospital staff was quickly evident and was most extraordinary. The problems dealt with during this decisive period are far too numerous and complex to be reviewed in this paper. The psychiatrist interviewed the patient in the hospital from October, 1953, to May, 1954, for a total of 87 hours. The patient seemed to take a new interest in everyday living. She ate a liberal, practically unrestricted diet without discomfort. The diarrhea and abdominal pain subsided completely with little or no medication. On Dec. 1, 1953, she developed homologous serum hepatitis, but recovered uneventfully by the end of December, 1953. The patient's amazingly good progress continued during the first four months of 1954. As psychotherapy continued, her personality changed from that of a whining, querulous, complaining child, to a more mature, self-assured, and pleasant young lady. This improvement was not complete, however, for at times the patient betrayed evidences of the fragile nature of her recently acquired emotional tranquility. This was clearly recognized and led to the recommendation that psychotherapy be continued for a long time, perhaps indefinitely.

On April 30, 1954, the patient returned home. She has been free of symptoms for the past year, the longest remission experienced thus far. Treatment has consisted of rest, with the occasional use of belladonna, phenobarbital, and vitamins. The patient has maintained contact by occasional long-distance telephone calls, most recently in May, 1955. She has not returned for further psychiatric interviews despite the recommendation.

Comment.—By the usually accepted standards of therapy, the course of this patient's illness, characterized by innumerable hospitalizations, hemorrhages, transfusions, continued diarrhea, and pseudopolyposis, amply justified the recommendation of total colectomy made elsewhere. The currently successful response to medical treatment may be attributed in part to the persistent and determined efforts of the attending physician and to the unusually skilled attention of the psychiatrist. Cortisone helped to control the acute phases and to reverse the progressive downhill course. Rectal hemorrhages severe enough to cause profound shock were terminated within several hours; yet, in retrospect, skillful psychiatric treatment, in contrast to the earlier indecisive and perhaps traumatic approach, was the major factor in the patient's response. The choice of a woman psychiatrist proved to be a happy one. The subsequent course of this complex case is difficult to predict. It probably will be determined by numerous factors: the patient's adjustment to the home environment; the attitude and wisdom of her parents; her reorientation to former friends; the continued attention and support of both physician and psychiatrist, and other less well-defined emotional and physical influences. Despite the remarkable progress to date, the patient remains an emotionally fragile individual, vulnerable to further recurrences of the disease.

Case 4.—P. K. was first seen by us in 1951, at the age of 16 years. In 1947 he had first noticed generalized, dull, abdominal pain followed by a loss of weight, easy fatigability, decreased appetite, and slowly increasing diarrhea and fever. Hospitalization resulted in no definitive diagnosis; treatment with penicillin was ineffectual. In the autumn of 1948 the patient was admitted to a tuberculosis sanitarium, where he improved with bed rest, liver extract, and occasional blood transfusions; he was released after six months because the suspected diagnosis of abdominal tuberculosis could not be confirmed. The patient remained well for five additional

months, but symptoms returned three months after starting school in September, 1949. Severe anorexia, bloody diarrhea, and rapid loss of weight necessitated hospitalization. A vacation in Florida produced temporary improvement. In October, 1950, continued rectal bleeding necessitated numerous transfusions. The persistence of symptoms resulted in his transfer to us in June, 1951.

Physical examination revealed an underdeveloped, emaciated boy, who appeared younger than his chronological age. He weighed 31.5 kg.; the blood pressure was 110 mm. Hg systolic and 90 mm. diastolic. The abdomen was protuberant and slightly tender; bowel sounds were increased. Several large external hemorrhoids and two deep anal fissures were noted. Proctoscopic examination for a distance of 12 cm. revealed a pale mucosa with no

Fig. 4 (Case 4).—Roentgen appearance of colon and terminal ileum.

granularity or friability. The erythrocyte count was 4,600,000 cells per cubic millimeter; the Hgb., 14.0 gm. per 100 cc.; the white cell count was 15,600 cells per cubic millimeter; the differential count was normal. Urinalysis disclosed slight albuminuria, occasional hyaline casts, and white blood cells. The feces were strongly positive for occult blood; no ova or parasites were found. The total serum proteins were only 4.4 gm. per 100 cc., with the albumin 2.1 and globulin 2.3. Serum electrolytes (milliequivalents per liter) were as follows: sodium 123, potassium 4.5, chlorides 89, and CO_2 28. The prothrombin time was 92% of normal. The absolute eosinophile count was 44. There was a 29% disappearance of Congo red dye from the serum. Roentgen examination of the gastrointestinal tract revealed a dilated terminal ileum with an abnormal mucosal pattern, loss of haustra, and pseudopolyposis throughout the colon (Fig. 4).

Treatment with a low-residue, nonlaxative diet, phenobarbital, belladonna, 8 gm. of sulfaguanidine, and 1,200,000 units of penicillin daily was ineffectual. The serum electrolytes were maintained with great difficulty. On June 26, 1951, the serum sodium was 126 and the potassium 3.6 mEq/liter. Supplementary salt, parenterally and orally, produced only transient improvement. On the 20th hospital day, 15 mg. of corticotropin was given intramuscularly every six hours; after 9 days of no improvement, 15 mg. was administered intravenously daily. The diarrhea promptly decreased; the temperature returned to normal, and the pulse declined to less than 100 per minute. However, the electrocardiogram revealed changes consistent with hypokalemia; the serum pH was 7.54. During this period of hypokalemic alkalosis there was profound muscle weakness and depression of the deep reflexes. Blood, appropriate electrolytes, and a decrease in the dosage of corticotropin were required to control the chemical disturbance. The daily caloric intake never exceeded 1700 Cal.

On Aug. 11, 1951, the patient complained of severe abdominal pain; the pulse rose to 160 per minute, and the temperature reached 44.0 C (104 F). The abdomen was distended, tense, and tympanitic; perforation of the bowel was feared. At operation, the peritoneal cavity contained a small amount of milky fluid; there was no obvious perforation. The terminal 20 in. of ileum and the entire colon from cecum to rectum were involved in a severe acute inflammatory reaction. A colectomy to the rectosigmoid and resection of the terminal ileum were performed in one stage. The patient received five units of blood during the operation and one unit daily for the next six days. His condition improved remarkably and he was afebrile in 24 hours. The ileostomy began to function on the fourth postoperative day. Cortisone was given on the 19th postoperative day, and the patient's oral intake of food rose from 800 to 8000 Cal. per day. Upon discharge from the hospital, on Sept. 19, 1951, he had gained 7 kg. of weight.

The resected bowel consisted of 50 cm. of ileum and 86 cm. of colon. The distal segment of the ileum was grossly ulcerated, with only a few small islands of surviving mucosa. The ileocecal valve was ringed by polypoid mucosal nodules resembling caruncles. The entire colon was ulcerated, with many islands of polypoid mucosa, particularly in the ascending colon. Microscopically, many of the ulcers were covered with an exudate; eosinophiles and lymphocytes were common in the granular bases of the ulcers, many of which had penetrated through the main muscle coats. In the proximal nonulcerated

portion of the ileum, mucosal deposits of amyloid material were found; there was no amyloid in the submucosa. The amyloid (stained metachromatically with methylrosaniline chloride [crystal violet]) surrounded many of the blood vessels and was deposited focally along the basement membrane; thus, its presence led to a blunting of the villi and a general thickening of the mucosa.

On Sept. 23, 1951, four days after discharge from the hospital, the patient returned because of nausea, vomiting, and colicky abdominal pain. An intussusception of the ileostomy was reduced with a tap-water enema. The patient improved temporarily, but the same abdominal distress returned 10 days later. The white cell count rose to 17,000, and there were signs of paralytic ileus. Laparotomy revealed a volvulus of the small bowel and multiple adhesions; after restoration of normal bowel continuity, recovery was uneventful. Twenty-five milligrams of cortisone daily was continued.

The third admission was on Jan. 9, 1952, again because of abdominal pain, severe apathy, and weakness of three days' duration. The blood pressure by palpation was 95 mm. of Hg systolic; there was a tachycardia of 120 per minute. The temperature rectally was 36.0 C (96.8 F). The patient was severely dehydrated. The sensorium was dull, and all reflexes were hypoactive. A presumptive diagnosis of Addisonian crisis seemed justified on the clinical evidence and the knowledge of amyloidosis of the small bowel. The patient responded to large doses of cortisone intramuscularly, desoxycorticosterone acetate, and saline infusions. The serum electrolytes (milliequivalents per liter) were as follows: sodium 121, potassium 4.5, chloride 91.2, and carbon dioxide 20.4; the blood pH was 7.32. Hematologic studies were normal except for moderate hemoconcentration. Urinalysis revealed a 2+ albuminuria with granular casts and doubly refractile fat globules (possibly amyloid bodies). The electrolytes rapidly returned to normal levels, and the patient's clinical status improved. Therapy on discharge included 50 mg. of cortisone and 3 gm. of sodium chloride daily.

He was admitted four days later, unconscious, in a severe and unmistakable adrenal crisis, with clinical findings of shock and a systolic blood pressure of 60 mm. of Hg. The pulse was feeble, with a rate of 160 per minute; the rectal temperature was 35.6 C (97.1 F). He responded well to the regimen previously described and within 12 hours had improved. It had been difficult clinically to identify the trigger mechanism initiating the two episodes of adrenal crisis. A serosanguinous discharge had been noted from the ileostomy opening, and there had been a progressive narrowing of the stoma. During the reconstruction of the ileostomy stoma, numerous fistulae between loops of terminal ileum were discovered. Eighteen inches of ileum was resected, and a few ileostomy opening was established. The resected bowel was similar microscopically to the section reported earlier, except for a decrease in the degree of amyloid infiltration. The patient was well for one week postoperatively, receiving 100 mg. of cortisone daily. On the ninth day, he experienced a severe grand mal type of convulsion, passed into a shock-like state, and was unconscious for several hours. Because of respiratory embarrassment and laryngeal stridor, an emergency tracheotomy was performed; the patient recovered uneventfully. He was maintained subsequently on diphenylhydantoin (Dilantin) sodium without further convulsive seizures. Occasional episodes of adrenal insufficiency required large amounts of cortisone and salt. Since revision of the ileostomy, the requirement for cortisone has decreased, as shown by the fact that since April, 1954, he has been maintained on 50 mg. of cortisone and 4 gm. of sodium chloride daily. A urea clearance test in June, 1954, was 64% of normal. The patient now weighs 47 kg., a gain of approximately 16 kg. in two and one-half years. The dietary intake averages 3000 Cal. per day. The blood pressure is 120/76. The urine now is free of casts and contains only a slight trace of protein. There is no evidence of anemia, and the serum electrolytes are normal. The patient tolerates the ileostomy well. His adjustment to the many difficulties has been remarkable and, except for the medications and the care of the ileostomy, he seems to be living a reasonably normal life.

Comment.—The difficulty at times in establishing the diagnosis of ulcerative colitis is again emphasized by this patient. Approximately four years elapsed and numerous empirical therapeutic measures were attempted unsuccessfully before the true nature of the process was recognized. This case also is representative of the small group of patients not responding to any medical therapy, with the disease progressively increasing in severity and apparently dealt with effectively only by operation. There seems little question that colectomy was a life-saving procedure.

The failure of occasional patients to respond to large doses of corticotropin intramuscularly and yet to respond to intravenous administration is of considerable interest. The steroid apparently may be partially inactivated by tissue enzymes, a difficulty obviated by the intravenous route. The intra-

venous administration also induces much more potent adrenocortical stimulation.

The present case is of interest also because of the unusual complication of amyloidosis. The Addisonian crises presumably are attributable to infiltration of the adrenal glands with amyloid. The epileptic seizures may have been caused in a similar manner, for the earliest sign of generalized amyloidosis may be grand mal convulsions, resulting from deposition of amyloid in the cerebral vessels. The kidneys presumably are involved only slightly, in view of the minimal abnormalities in the urine. The electrolyte deficiencies presented a major therapeutic problem and were unusually severe, probably because of the persistent diarrhea and the adrenal insufficiency, initially unrecognized but subsequently responding characteristically to salt, desoxycorticosterone acetate, and cortisone. Corticotropin was relatively ineffectual, owing presumably to the inability of the adrenal glands to respond to stimulation.

This case also illustrates some of the problems complicating colectomy and ileostomy. Colectomy and ileostomy are not preferred treatment in ulcerative colitis at any age; the operation is distinctly undesirable in children and young adults. Yet, in the present instance, emergency surgery proved to be a life-saving measure. However, intussusception and volvulus involving the terminal segment of small bowel occurred within a few weeks of each other. Spontaneous small bowel fistulas and diarrhea developed, probably precipitating two Addisonian crises. Reconstruction of the ileostomy stoma was necessary on several occasions, because of stricture. The problems of stenosis of the ileostomy, partial obstruction, fistula formation and other difficulties associated with the establishment of an ileostomy are frequent and important.

COMMENT

Despite extensive investigation, the etiology of ulcerative colitis remains unknown. Many causes have been suggested,‡ including bacterial and viral infections, nutritional deficiencies, allergy, hypersensitivity mechanisms, alterations in the ground substance of the connective tissue of the colon, destructive enzymes acting upon and within the mucosa and submucosa of the bowel wall, and neurogenic and psychogenic disorders. The selected cases described in this report tend to emphasize the role of emotional disturbances. On the other hand, the psychogenic aspects may represent merely identifiable contributory influences rather than fundamental causes; the evidence is impressive but largely circumstantial. The relatively high incidence of ulcerative colitis in young adults and the occurrence of the disease in children may reflect important pathogenic mechanisms, perhaps tissue hypersensitivity; the possibility of individual susceptibility to the disease on this basis is an interesting concept, worthy of further study. Careful, prolonged observation of the disease in children thus provides a valuable opportunity to study the illness in its earlier stages, perhaps under circumstances less complicated than in the adult.

The diagnosis of ulcerative colitis is suggested by a history of diarrhea, usually bloody; cramping abdominal pain; fever; anemia; malaise, and weight loss. On the other hand, the consistency of the bowel movements may be normal when the process is limited to the rectum and is relatively superficial. In approximately 95% of cases with active colitis, the rectum and sigmoid are diffusely inflamed, edematous, granular, and bleeding; the rectal ampulla often contains bloody, watery fecal material. Roentgen examination in most instances demonstrates loss of the normal haustral markings, stiffness and narrowing of the colon, an irregular pseudopolypoid mucosal pattern, ulceration, and serration of the barium outlined colon. These changes involve varying portions of the large bowel from the rectum to the ileocecal valve; the entire colon is affected in 50% of cases; the adjacent terminal ileum is diseased in 15% or 20% of cases. In approximately 15% or 20% of patients, the bowel appears normal roent-

‡ References 5-7.

genologically, despite evidence of colitis at proctoscopy. In some instances, the roentgen features may be so mild as to avoid recognition except after the most careful scrutiny. Decreased distensibility of the rectum, extremely fine marginal serration, or slight alterations in the mucosal pattern may be the earliest and the only x-ray findings. In the absence of roentgen changes, the diagnosis depends chiefly on the proctosocpic findings. In patients with regional colitis, the x-ray examination usually is the most important diagnostic aid. At times, repetition of these procedures, a more careful roentgen examination, or more complete proctoscopy may be necessary to establish the diagnosis. The laboratory studies are valuable chiefly to exclude specific pathogenic bacteria or parasites; positive results have been rarely noted, in our experience.

Ulcerative colitis is a chronic disease, with remissions and relapses occurring at unpredictable intervals.[8] The complications are numerous and varied; they appear to be as frequent in children as in adult patients. In the present group, they include perirectal abscess with fistula formation and erythema nodosum in Case 1, recurrent anemia in Case 2, arthritis and recurrent hemorrhages in Case 3, and the unusual problem of amyloidosis with adrenal insufficiency in Case 4. Polyps and carcinoma of the colon, perforation of the bowel, hepatitis and cirrhosis, and retarded physical development also have been observed. The persistently active colitis in children often is very resistant to therapy. At times, however, there may be a striking cessation of symptoms, with return to excellent health; the factors responsible for this change remain as obscure as the origin of the disease itself; nevertheless, the observation again emphasizes the potential for healing in this disease.

The treatment of ulcerative colitis continues to be symptomatic, adapted to the needs of the individual patient, and prolonged.§ Medical management seems indicated in 80% or 90% of adult cases and in practically all children with the disease. As in the adult, the objectives of therapy are adequate rest, restoration of normal bowel activity, elimination of infection, restoration of nutrition, and resolution of the emotional problems apparent in many patients.[12] Mild ulcerative colitis often responds to treatment with rest in bed and a bland, nutritious diet, avoiding mechanical and chemical irritants but providing adequate quantities of protein, and the use of sedatives and antispasmodics, such as phenobarbital (15-30 mg.) and belladonna extract (7.5 mg.) three or four times daily; many other sedatives and antispasmodics are available for this purpose, as described elsewhere.[8] Since atony of the colon has been noted very occasionally in patients given large doses of potent antispasmodics, their routine use in ulcerative colitis probably should be avoided. The numerous watery bowel movements may cause depletion of sodium, potassium, and chloride, requiring the administration of appropriate solutions of electrolytes, glucose, and water. The combination of electrolyte deficiency and hypoproteinemia is best treated by transfusions of whole blood. Iron-deficiency anemia, a common occurrence among children with ulcerative colitis, responds effectively to the intravenous administration of saccharated oxide of iron. The development of a hemolytic anemia in several children has necessitated the use of cortisone.

Sulfonamides are prescribed to control secondary infection and with the hope of eliminating unidentified bacterial causes of the disease. The compounds prescribed most frequently in ulcerative colitis include sulfaguanidine, salicylazosulfapyridine, sulfadiazine, and phthalylsulfathiazole (Sulfathalidine); many other sulfonamides, singly and in combination, are available. Beneficial results may be noted initially; occasionally they are sustained; frequently the response is temporary. Bacterial resistance and drug sensitivity may develop, further handicapping chemotherapy. Penicillin and streptomycin

§ References 9-10.

may be administered for the same purpose as sulfonamides; the clinical response occasionally is excellent. Favorable results have been reported also with various antibiotics. However, since these compounds may produce disturbing gastrointestinal symptoms, including "antibiotic colitis," their routine use in ulcerative colitis appears undesirable.

Although the response to conventional medical therapy as outlined often is favorable, many patients, usually those with extensive disease, do not improve adequately or consistently. In such resistant cases, corticotropin intramuscularly, hydrocortisone orally, and, to a lesser degree, cortisone and prednisone by mouth, may be useful adjuncts.‖ These compounds serve as "therapeutic bridges," reversing an unfavorable trend, initiating and accelerating the process of recovery, and generally facilitating the "total" management of the disease. Steroid therapy requires careful supervision in the hospital or at frequent visits in the office. Sulfonamides are administered concurrently, and the serum electrolytes are measured frequently. Although various complications have been reported in the literature, we thus far have encountered serious problems in few patients. Perforation of the cecum has been observed in only 1 among more than 200 patients, the complication antedating the administration of steroids; only 2 instances of peptic ulcer have been noted in the same series. The quantity of corticotropin or hydrocortisone and the duration of treatment vary with the individual patient; therapy may be terminated gradually or continued for many months. No special problems have arisen thus far during the use of these compounds in children. Recurrences of ulcerative colitis are rather frequent, as with the usual forms of therapy, and the response to repeated courses of treatment may be progressively less favorable. On the other hand, steroid therapy may be the most effective method of maintaining the health of the young patient with colitis without surgery. The roles of corticotropin, hydrocortisone, and cortisone are well illustrated by the four cases of the present report. They do not cure ulcerative colitis, prevent recurrences, or replace established methods of treatment. Nevertheless, under properly controlled conditions and in adequate amounts, they are helpful adjuncts.

Surgical intervention is necessary in 10% or 15% of adult patients with ulcerative colitis, the figures varying somewhat with the severity of the cases under consideration. The usual indications are serious complications and the lack of response to adequate medical management, as discussed elsewhere.¶ Surgical treatment seems rarely indicated in children and then only for the most serious problems, as in Case 4. The operation of choice in adults is total colectomy and ileostomy in one or two stages. The advances in surgical technique and in preoperative and postoperative care have been very great; nevertheless, the operation is not to be undertaken lightly at any age and certainly not in children. Despite recent technical improvements, the problems of the ileostomy stoma are frequent and at times serious. Ileostomy alone usually is not recommended, although the procedure occasionally is undertaken in selected cases. Segmental resection of the colon may be indicated in patients with limited involvement of the colon.

Despite lack of knowledge of the etiology of ulcerative colitis, the progress in medicine and surgery has decreased the mortality rate from this disease in the past 50 years from 50% to 5%. Almost all young patients with ulcerative colitis can be maintained in satisfactory or excellent health by continued careful medical management. Occasionally, there may be striking reversibility of the diseased colon to normal or near normal[15]; in all probability many patients retain this potential for recovery. Continued and intensified experimental and clinical investigation may provide the solution to this complex problem for all patients with the disease.

‖ References 13 and 14.

¶ References 5 and 9-11.

SUMMARY AND CONCLUSIONS

Ulcerative colitis in children is not uncommon and follows a course similar to that in adults. The disease should be suspected in patients with unexplained fever, anemia, and abdominal pain, with or without bloody diarrhea. Four selected cases are described in detail, illustrating certain psychiatric and therapeutic aspects as well as various complications, such as rectovaginal fistula, electrolyte disturbances, and amyloidosis with adrenal insufficiency. The clinical course in these patients again emphasizes the importance of prolonged, comprehensive medical treatment, skillful psychotherapy, the adjunct value of steroid therapy, and, on occasion, the life-saving role of surgery.

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Gangrene of the Extremities in Infants Subsequent to Intravenous Therapy

Precautions in Technique and Report of Five Cases

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Intravenous therapy for debilitated, cachectic, or septic infants may be the inciting factor in local tissue necrosis and partial or total gangrene of one or more extremities. It is likely that the hazard is greatest in the newborn, especially when birth has been premature. Although untoward consequences to intravenous therapy in children are rare, at the Cook County Children's Hospital, five cases of infant gangrene of the extremities subsequent to cannulization have been gathered since 1948. All instances were in critically sick infants and took place after the procedure hereinafter referred to as cutdown had been performed.

CUTDOWN

Definition.—To obviate the possibility of differences in interpretation owing to local usages, it may be well to define our term.

Cutdown is employed to embrace the procedures of venipuncture, incision over the vein, venesuture, and the insertion of a cannula for intravenous therapy, which is usually required for children when major surgery is scheduled or in the presence of pneumonia, diarrhea, and septic and cachectic conditions.

Incidence.—An average of 550 cutdowns are performed for intravenous therapy among 6700 admissions a year in the Cook County Children's Hospital.

Technique.—The first cutdown is ordinarily performed by the resident surgeon, with the succeeding cutdowns done by the intern under the supervision of the resident.

The cutdown procedure, as applicable to the leg, is outlined herewith:

1. The lower leg and foot are scrubbed with medicinal soft soap (green soap) for 10 minutes.

2. The saphenous vein is located just cephalad and anterior to the medial malleolus. A sterile sheet is laid over the area.

3. A small transverse incision is made over the vein, and all connective tissue is stripped away. It is emphasized that incisions need only be small and should not be deep, because deep incisions may involve the arterial system.

4. Small mosquito forceps are inserted under the vein, and the distal part of the vein is tied off with an absorbable surgical suture (gut) ligature.

5. The proximal vein is lifted and made taut by passing a gut suture under it and holding it above with forceps.

6. A transverse opening is then made into the veins with the use of fine scissors; from one-half to three-fourths of the circumference of the vein must be incised.

7. A polyethylene catheter of proper size is threaded through the vein for about an inch or more.

8. The suture from above is tied down around the vein through which the catheter has been inserted.

9. One or two black nonabsorbable surgical (silk) sutures may be placed across the skin incision on each side of the catheter.

10. A sterile dressing is placed over the area, and a padded splint is placed on the posterior aspect of the leg. The surgeon applies narrow strips of tape to bind the dressings down over the cutdown site.

Antibiotics are not given for this procedure per se, but in most instances are administered for a concomitant infection.

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The cutdown procedure as described is identical for the area distal to the anatomic snuffbox in the wrist, for any prominent vein in the cubital fossa, or for the cephalic vein in the upper third of the arm.

In our experience fewer infections occur when cutdowns are performed in the area of the wrist or forearm rather than in the leg.

REPORT OF FIVE CASES

CASE 1.—E. R., a premature Negro boy, born at 6-month term in Cook County Hospital on Oct. 22, 1949, weighed 2 lb. 4 oz. One week after birth, because the infant was in poor condition, intravenous therapy was ordered.

A cannula was inserted in the region of the elbow. Three days later the left forearm became cold and cyanotic. The following day the fingers were deeply discolored. The cannula was thereupon removed and was found to have entered the left brachial artery on insertion.

Procaine hydrochloride, 5 cc. of 1% solution, was injected into the left stellate ganglion, and hot wet dressings were applied to the arm daily. By the first of November, 11 days after birth, moist gangrene, later becoming dry, appeared. The infant died two days later (Figs. 1 and 2).

CASE 2.—R. B., a Negro boy, was born prematurely at 6-month term on March 5, 1949, of a mother who had had interpartum sepsis. The first stage of labor had been of 32 hours' duration. The infant weighed 2 lb. 4 oz. at birth. He was cyanotic and limp. Distention was extreme, and persistent vomiting resulted in dehydration requiring intravenous therapy at 18 days after birth.

Course After Cutdown.—On March 23, after an unsuccessful cutdown attempt over the left foot, a dorsal cutdown was made over the right wrist (Fig. 3). A cannula was inserted and left in place until April 1. On April 3 the right hand was edematous, with black discoloration of the palm and all fingers except the index finger. Evidence of gangrene of the third, fourth, and fifth fingers soon appeared, with involvement of the distal pulp of the thumb and index finger. Two weeks later excision of an eschar on the index finger was required.

The diagnostic impression on surgical consultation was of a venous thrombus or arterial spasm. A stellate ganglion block was performed with good results. Heparin was administered and refrigeration applied. On April 4 the thumb fell off; by April 30, all fingers except the index finger were missing. By May 2, a left shoulder abscess had formed, and acute bronchitis added to the complications.

Blood cultures made on March 10 and May 25 showed nonhemolytic Staphylococcus aureus.

Fig. 1 (Case 1).—Gangrene in arm of premature infant after accidental insertion of cannula into left brachial artery.

Fig. 2 (Case 1).—Close-up of gangrenous area.

Treatment.—Treatment consisted of oxygen, nikethamide (Coramine), streptomycin, sulfadiazine, intestinal absorbent containing kaolin and pectin (Kaopectate), lactate, plasma, 5% dextrose, and procaine penicillin G (Crysticillin). The patient gradually recovered.

Follow-up.—Three years later, Nov. 15, 1952, when the patient was seen on readmission because of mental retardation, the hand remained essentially as illustrated in Fig. 3.

Comment.—This is our only living patient of the series of five infants who had had gangrene subsequent to cutdown procedures.

Fig. 3 (Case 2).—Cutdown over left foot unsuccessful; second cutdown dorsal over right wrist resulted in gangrene. Only patient in series to survive.

Case 3.—R. L., a Negro girl aged 15 months, was admitted on Aug. 13, 1948, because of recurring upper respiratory infections, loss of weight, and a refractory skin condition. Interstitial pneumonitis and duodenal ulcer were disclosed on examination.

History.—Two days after birth, superficial erosions had appeared at points of contact. Multiple facial excoriations and dry scaly skin suggested congenital syphilis or desquamative erythroderma. Kahn reactions were positive on one occasion, negative on three others. Roentgenologic survey revealed periosteal reaction and medial elevation

Fig. 4 (Case 3).—Gangrene of left foot, site of cutdown.

Fig. 5 (Case 4).—Gangrene of right foot and ankle. Cutdown was done in region of medial malleolus of right leg.

Fig. 6 (Case 5).—Fatal case of dextrocardia complicated by pneumonia, sepsis, and local gangrene of the entire dorsum of left foot, site of cutdown for intravenous therapy.

of the inner periosteum of the tibia; four months later extension to other long bones was observed. The general appearance was that of congenital syphilitic periostitis. The skin condition became progressively worse, with easily bleeding abrasions.

Course After Cutdown.—On admission a cutdown was made on the left foot. The foot turned blue and cold and eventually became gangrenous (Fig 4). Lumbar sympathectomy was ineffective. On Sept. 9, 1949, bilateral explosive keratitis occurred. Two days later, respirations became shallow. Sept. 13, the patient did not respond to therapy of vitamins, subcutaneous fluids, or antibiotics. She died 16 months after birth.

Autopsy.—A pulmonary infarct disclosed at autopsy probably arose from the thrombophlebitis at the site of the cutdown. A lung abscess apparently was the immediate cause of death.

Case 4.—L. R., a Negro girl aged 6 months, was admitted on Sept. 21, 1952, because of diarrhea and dehydration.

Cutdown.—A cutdown was done on Sept. 26 in the region of the medial malleolus of the right leg. Polyethylene tubing was inserted. Repeated intravenous fluids were given, averaging from 700 to 1100 cc. a day, including 5% dextrose, Ringer's solution, lactate, vitamin C, vitamin B_1, and whole blood. On Sept. 29, the child was convulsing, and calcium gluconate, 10 cc. of 5% solution, was added to the intravenous fluid. Oct. 1, the temperature rose to 102 F. The abdomen became distended, and infection of the lower right leg ensued. Cellulitis and bleb formation resulted.

Terminal Course.—Oct. 2, the right foot and ankle became cold and blue, and the pulses were not palpable. There was some blanching with return of blueness. The entire leg and thigh were swollen. Popliteal pulsation about the ankle was absent. Several abrasions preceded gangrene (Fig. 5). The child died two days later.

Case 5.—A. H., a Negro girl aged 3 months, was admitted for surgical correction of a transposition of the vessels of the heart. A cutdown of the left foot was done for intravenous therapy. A salt-free protein hydrolysate (Amigen), 70 cc., was used in the intravenous fluid. Local gangrene of the entire dorsum of the left foot ensued (Fig. 6).

*Infant Gangrene**

Case	Race	Sex	Age at Time of Cutdown	Location	Associated Medical Condition	Result	Autopsy Finding
1	N	M	1 wk.	Left hand Left forearm	Premature infant	Death	Thrombosis; brachial artery
2	N	M	18 days	Right hand	Cerebral birth injury Gastroenteritis (severe)	Loss of all fingers except index & part of thumb	Thrombosis; radial artery
3	N	F	15 mo.	Left foot Left leg	Interstitial pneumonitis Lung abscess Duodenal ulcer Congenital syphilitic exfoliative dermatitis	Death	.....
4	N	F	6 mo.	Right foot Right leg	Severe gastroenteritis	Death	.....
5	N	F	3 mo.	Left foot	Congenital transposition of heart vessels	Death	.....

* Gangrene occurred within a few days of cutdown in all cases.

When the resident physician removed the tissue necrosis, he exposed the tendons and a thrombosed vein on the surface of the foot. The local area healed by secondary intention, but the child died two weeks later from dextrocardia complicated by pneumonia, sepsis, and gangrene.

PATHOGENESIS

The etiology of infant gangrene has been diversely ascribed to a long list of observed relationships: traumatic delivery; rachitic pelvis; parietal hematoma; version and extraction; brow presentation; prolonged labor; maternal prenatal fall; amniotic bands; wrapping of the cord around the neck; asphyxiation at birth; cyanosis; congenital heart anomalies; thrombosis of patent ductus; long bacilli in portions of thrombi; meningomyelocele; diabetes mellitus; angiospasm; endarteritis obliterans; thickening of endothelium of anterior tibial artery; neurotic angiosclerosis; periarteritis; periphlebitis associated with endophlebitis; edema of media of vessels; chlorosis; congenital syphilis; Raynaud's disease; liver impairment; infarcts of the liver, spleen, and kidney; infected emboli from umbilical vein or artery or infected navel; septicemia from such diseases as exanthemata and arteritis accompanying sepsis; septum arteriorum; intimal agglutination; "arterial occlusion during a critical illness with accompanying dehydration, emaciation, fever, and infection with apparent toxicity" [1]; overhydration in acute illness [2]; spontaneous idiopathic gangrene "with cyanosis following femoral venipuncture, thought to be due to spasm of the accompanying artery."[1]

It is not the intention of this paper to present a review of the literature. It is relevant to comment, however, that an evaluation of 96 cases reported permitted no etiologic common denominator to be drawn. Only the age factor is suggestive, for the most frequent occurrences are in young, usually neonatal infants, often of premature birth. It is feasible, therefore, that one explanation of gangrene, at least in premature and newborn infants, lies in this time of onset, when normal circulatory readjustments are at best demanding. In his excellent book, Clement Smith [3] explains the mechanism:

> There exist certain definite, although poorly measured, differences between the vascular system in infancy and in adult life, and most of these are especially noteworthy at the neonatal stage of development. After the functional adjustment from the fetal to the extra-uterine circulation has been made, there remain peculiarities in the distribution of the blood. [There is a] pooling of blood in the abdominal organs, especially the liver and the spleen, which are frequently palpable in the normal full-term infant. The consequence is a poor distribution of blood to the periphery. As the fetus grows larger and more mature *in utero*, its capillaries become more resistant to pressure. It is interesting that after birth the development seems to be reversed as though the fetus were supplied with an increasing resistance in preparation for meeting the stresses of birth.

For that reason,

> Capillary hemorrhages observed in the skin of a mature baby after birth must be taken to indicate either a serious departure from the normal integrity of vessel walls, an unusually difficult delivery, or an abnormality of the blood itself allowing it to ooze through a capillary wall capable of retaining ordinary blood.

It will be borne in mind, moreover, that many of the babies with gangrene are not mature but premature, so that in those cases, capillary resistance has not been established in utero; hence,

> Capillary networks as studied in the skin, appear to be coarse and to lack the finer control mechanisms they acquire later. The number of capillaries is smaller and the resistance of their walls weaker at premature than at full-term birth.

Dr. Chaddis,* a pediatrician of Argentina, has succinctly described the mechanism in infants as "labile vasomotor system which may cause the sudden vascular phenomenon of spasm with ensuing thrombosis, gangrene, and death."

Among many other clinicians, Martin and Shore [4] have observed the occurrence of spasm and then infection, or infection and then spasm, both producing tissue death. Any disturbance that interrupts the arterial blood supply to the extremities [5] may initiate an

* Chaddis: Personal communication to the authors, November, 1952.

irreparable downward course, with deaths seeming to be "directly proportional to the extent and location of the gangrene." [1] In the older age group there is unquestioned relationship between cardiovascular failure and the occurrence of spasm or occluding thrombosis or emboli during crucial illness.[1]

Other contributory factors are dehydration, cachexia, fever, general sepsis, perhaps too rapid and intense intravenous therapy leading to overhydration,[2] and always the presence of infection to initiate the course from the onset of gangrene to death. Anything that alters the integrity of the minute vessels of the extremities, such as infection, is likely to result in capillary thrombosis and gangrene.[4]

SUMMARY AND CONCLUSIONS

In two of the five cases of gangrene following intravenous therapy in desperately sick infants in our series, the babies had been born prematurely. A high percentage of 96 cases reviewed in the literature are of premature births.

There was one case of congenital syphilis in our series, one case of congenital transposition of heart vessels, and three cases of severe general sepsis; infection followed cutdown in all cases.

Apparently neonatal spontaneous gangrene is especially referable to long and difficult labor. All cases of infant gangrene appear to be associated with infection. A third category, as in our fifth case, is that of congenital anomalies, or of "amorphologic maldevelopment."[1]

Particular care should be given to those infants with severe general sepsis, cachexia, and poor tissue nutrition. Lowered resistance in infections is undoubtedly one cause of poor vasomotor response in infants and contributes to ultimate local tissue death even when the outcome is not fatal to the child. Every aseptic safeguard should be exerted against inviting local infection by careless procedure and thus overburdening the already critically ill infant.

Careful handling of tissues for venipuncture is necessary, and especially for incision over a vein, which is imperative not only to prevent infection but to prevent accidental severance of an artery. The vessels should be exposed meticulously, with gentle introduction of the needle or polyethylene tube. The step-by-step technique for cutdown as defined has been outlined with emphasis on the need for rigid asepsis.

Before intravenous therapy is instituted for the sick infant, one should weigh the status of the cardiovascular system and proceed cautiously in the face of any observable signs or deducible implications of circulatory disturbance or inadequacy; for example, the age of the child is indicative, for the younger the sick infant the greater the hazards of emboli or thrombosis. Vasomotor instability of the tissues invites infection, gangrene, and death of tissues or even of the child.

Both dehydration and overhydration are dangerous. Of the two, Gross and Ferguson [2] believe overhydration to be the greater danger; they suggest that, when intravenous therapy is necessary, introduction of fluids should not be overzealous. On the other hand, febrile dehydration may augment the coagulability of the blood.[1] Efforts must be directed toward controlling both tenuous conditions.

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Blood Cell Values for Healthy Adolescents

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Published data on the normal blood picture in adolescence are relatively scarce and show considerable disagreement.* In some instances the observed differences undoubtedly are attributable, at least in part, to the difference in the altitude at which the subjects were residing; in others no such ready explanation is available. Furthermore, in some of these data a wide range of hemoglobin values and red cell counts is reported for each age group. The question may be raised whether such marked differences represent normal variations and should be expected to occur in a group of subjects all of whom are in superior health.

In September, 1947, and again in 1949, we had the opportunity of studying the blood picture of a highly selected group of healthy rural youths. These were the 4-H Club boys and girls who had been chosen by the local physicians as the health champions of their respective counties in Minnesota. These youths were brought in groups to the laboratory throughout the day, where highly skilled medical technologists secured the necessary blood samples and made the various determinations. In the two years of the study, data were obtained on 110 boys, ranging in age from 12 to 21 years, and on 130 girls, ranging from 12 to 20 years.

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METHODS

Blood samples were secured from a free-flowing finger puncture. Hemoglobin determinations were made in duplicate; the alkaline hematin method and National Bureau of Standards certified hemoglobin pipettes were used. The samples were read in a Coleman Spectrophotometer which had been calibrated by means of the Van Slyke and Neill oxygen-capacity method.

Since a large number of red cell counts had to be made in one day, it was decided to use the Blum [8] photoelectric method for this determination. The galvanometer readings were converted into the number of erythrocytes per cubic millimeter from a chart based on a carefully prepared calibration curve. In about half of the cases, erythrocyte counts also were made, using the usual counting chamber method. A comparison of the results obtained by these two methods will be presented at a later date.

Mean red cell diameter was determined by measuring 100 cells on each of two dry, stained smears for each subject. The horizontal diameter of all normal cells in a field was measured, with use of a calibrated Bausch and Lomb filar micrometer.

For the estimation of reticulocytes a film of an alcoholic solution of brilliant cresyl blue was spread on clean slides and allowed to dry. Duplicate preparations were made for each subject by spreading a thin blood film over the stain and incubating in a moist chamber. At least 1000 red cells were counted for each determination, from which the mean percentage of reticulated cells was calculated. Mean corpuscular hemoglobin was computed using the Wintrobe [9] formula.

RESULTS AND COMMENT

The values for the mean, standard deviation, and range for hemoglobin, red cell count, and mean corpuscular hemoglobin for the boys and girls in each age group are given in Table 1.

The lowest mean hemoglobin value for the boys, 13.0 gm. per 100 ml. of blood, was secured for the 12-year-old group. Thereafter distinctly higher values were noted, reaching a maximum of 15.1 gm. at 16 years of age. The means for the 17- and the 18-

to-21-year-old groups were slightly, but not significantly, lower. The variation within age groups, as shown by the range of values, was from 2 to 3 gm.

Of the various studies reported in the literature, that by Wiehl [3] would seem most nearly comparable to the present study. Her subjects were students in a private school who came from high-income families. It might be expected that these subjects would be in better physical condition than boys and girls in the general population.

A comparison of the mean hemoglobin values secured in the present study on healthy rural youths in Minnesota with those reported by Wiehl for private-school boys residing in New York City, shows that the Minnesota values are somewhat lower. The differences vary from 0.6 gm. in the 12-year-old group to 0.9 gm. in the 15-year-old group. The New York boys were apparently a year advanced in hemoglobin level as compared with the Minnesota boys. The level attained by the Minnesota youths at age 16 was reached by the New York group at age 15. The variations within the various age groups, as shown by the standard deviations, were very similar in the two studies.

For red cell counts also, the lowest mean value, 4,240,000/cu. mm. of blood, was observed in the 12-year-old group. Increases occurred with considerable regularity with advance in years, attaining a level of 4,850,000 in the 16-year-old group. This value is in fair agreement with Wintrobe's suggested normal for boys 11 to 15 years of age, of 4,800,000. However, the values observed in the present study were in most instances more than 1,000,000 lower than those secured by Wiehl for comparable age groups in New York City.

TABLE 1.—*Hemoglobin, Red Cell Count, and Mean Corpuscular Hemoglobin Values for 4-H Club Health Champions in Minnesota*

Age, Yr.	Cases, No.	Hemoglobin, Gm./100 Ml.			Red Cell Count, Millions/Cu. Mm.			Mean Corpuscular Hemoglobin, $\mu\gamma$		
		Mean	S.D.	Range	Mean	S.D.	Range	Mean	S.D.	Range
Boys										
12	6	13.0	0.71	12.0-13.9	4.24	0.21	4.00-4.52	30.7	1.21	30.0-32.6
13	18	13.8	0.75	12.5-15.1	4.44	0.25	4.05-4.98	31.2	1.03	29.6-33.0
14	15	14.2	0.76	13.0-15.6	4.62	0.26	4.20-5.17	30.8	0.86	29.7-32.3
15	19	14.2	0.88	12.6-15.8	4.67	0.31	4.23-5.24	30.4	1.20	28.7-33.5
16	17	15.1	0.76	14.1-16.7	4.85	0.36	4.28-5.68	31.1	1.14	29.4-33.9
17	18	14.9	0.73	13.1-15.9	4.88	0.41	4.11-5.69	30.7	1.34	27.9-32.9
18-21	17	14.9	0.69	13.4-15.6	4.86	0.27	4.28-5.29	30.4	0.96	29.3-32.7
All	110	14.4	0.92	12.0-16.7	4.69	0.36	4.00-5.69	30.8	1.12	27.9-33.9
Girls										
12	13	13.0	0.61	12.1-14.0	4.31	0.17	4.08-4.56	30.1	0.70	29.0-31.3
13	11	12.8	0.61	11.9-14.2	4.26	0.20	4.00-4.77	30.1	0.78	29.1-31.3
14	29	13.1	0.62	12.1-14.6	4.34	0.22	3.88-4.74	30.3	1.09	28.6-32.4
15	25	13.1	0.75	12.0-14.5	4.31	0.28	3.86-4.92	30.4	1.09	28.4-32.5
16	20	12.7	0.81	11.0-14.0	4.19	0.27	3.56-4.65	30.4	1.19	28.6-33.0
17	19	12.9	0.59	12.0-14.6	4.20	0.25	3.74-4.81	30.6	0.98	28.7-32.6
18-20	13	13.3	0.48	12.5-14.0	4.34	0.20	4.02-4.74	30.7	0.89	29.2-32.1
All	130	13.0	0.67	11.0-14.6	4.28	0.24	3.56-4.92	30.4	1.01	28.4-33.0

Mean corpuscular hemoglobin values by age groups were surprisingly constant in the present study, with no indication of change with age. The mean for all age groups was 30.8$\mu\gamma$. This is in contrast to the results reported by Wiehl, who obtained a mean value of 24.0$\mu\gamma$ for 12-year-old boys, with increases to 27.4$\mu\gamma$ in the 17-to-18-year-old group. The pronounced difference in the hemoglobin content of the individual red cells of these two groups of selected subjects may be attributed either to a difference in the size of the individual cells or to the degree of saturation of the cells with hemoglobin. In the present study, on the basis of cell-diameter measure-

ments, there was no indication of change in cell size with age. Wiehl, on the other hand, noted significant increases in mean corpuscular volume with advance in years, which would seem to indicate that the red cells increased in thickness during adolescence.

For the girls, the mean hemoglobin value for the 12-year-old group was 13.0 gm., which was the same as that for the boys in this age group. Thereafter distinct sex differences are apparent. Whereas the values for the boys increased with age, those for the girls remained essentially unchanged or showed small decreases. The low value, 12.7 gm., was noted in the 16-year-old group, with recovery to 13.3 gm. by 18 to 20 years of age. Osgood [1] found that the hemoglobin levels of the two sexes diverged sharply at 14 years, the girls reaching the adult level at this age and the boys, two years later. For these Minnesota youths, sex differences in hemoglobin and red cell counts are evident beginning at age 13.

The somewhat smaller standard deviations secured for the girls than for the boys indicate that there is less variation within age groups among the former than among the latter. The differences in physiologic age among boys in a given age group are undoubtedly a factor of importance in this connection. Whereas the girls had reached a plateau in hemoglobin level at age 12 and showed no increases until 18 to 20 years of age, when a slightly higher mean value was secured, the hemoglobin levels of the boys did not stabilize until age 16.

A comparison of the data in the present study with those secured in an earlier study,[6] on a group of 258 high school girls residing in Minnesota, shows that this group of rural adolescent girls had hemoglobin values which averaged 0.8 gm. higher. The girls in the earlier study were selected by the school physician as being in good health, but it is evident that their hemoglobin levels were less satisfactory than those of the girls in the present study. Since both studies were carried out in the early fall, seasonal variation in hemoglobin level, such as has been reported by Platt and Freeman,[10] cannot account for the observed differences between the two groups. However, it should be pointed out that in the earlier study the Newcomer method was used for the determination of hemoglobin. No direct comparison of these two methods has been made in this laboratory, and it is possible that the difference in method may account for the observed differences in hemoglobin level.

The mean red cell count for the 12-year-old girls was essentially the same as that for the boys in this age group. However, no significant increase occurred with age. From this it would appear that Minnesota girls have attained both the hemoglobin level and red cell count characteristic of the early adolescent years by the time they are 12 years old.

A comparison of the red cell counts secured for the girls in this study with those for the girls observed by Wiehl again shows very much higher values for the New York group. This divergence between the two groups is reflected in the mean corpuscular hemoglobin values. For the girls, as for the boys, mean corpuscular hemoglobin averaged between 30.0 and 31.0$\mu\gamma$ for each age group in the Minnesota study, with no significant variation with age. Wiehl, on the other hand, obtained a mean corpuscular hemoglobin value for her 12-year-old girls of 26.0$\mu\gamma$, increasing with age to a maximum of 27.2 in the 16-to-17-year-old group. She also reported highly significant differences between the sexes at ages 12 and 13 years.

In Table 2 are presented the data for red cell diameter measurements and reticulocyte counts. The mean cell diameter for the boys was $7.88\pm0.18\mu$ and for the girls $7.94\pm0.15\mu$. No significant change in cell size associated with age was observed in either the girls or the boys. These mean values are considerably higher than the $7.5\pm0.3\mu$ suggested by Wintrobe as the normal value for adult males and females. The diameter data presented herein are based on the measurement of cells in a dry film. This method gives higher values than when based on a moist film and may account for this discrepancy. However, the variability noted

in the present study, as shown by the standard deviation, was considerably less than the 0.3μ suggested by Wintrobe for adults. The mean cell diameter for the girls in the present study is in agreement with the findings on high school girls in our earlier study, for whom a mean cell diameter of 7.90±0.20μ was secured.

For the boys, the lowest mean cell diameter for any subject was 7.35μ and the highest, 8.28μ. For the girls, the comparable values were 7.62μ and 8.36μ.

Reticulocyte counts for both the boys and girls averaged 1.0%. Although variations within age groups were wide, no difference between the boys and girls was evident, nor was there any indication of an age factor in either group.

Table 2.—*Red Cell Diameter and Reticulocyte Values for 4-H Club Champions in Minnesota*

Age, Yr.	Cases, No.	Red Cell Diameter, μ			Cases, No.	Reticulocytes, Per Cent		
		Mean	S. D.	Range		Mean	S. D.	Range
Boys								
12	6	7.95	0.15	7.78-8.14	6	0.96	0.18	0.68-1.20
13	18	7.87	0.17	7.57-8.18	16	0.94	0.27	0.35-1.40
14	15	7.84	0.19	7.35-8.12	13	0.98	0.37	0.20-1.48
15	19	7.91	0.19	7.62-8.28	18	1.03	0.46	0.40-2.51
16	17	7.86	0.20	7.39-8.12	16	1.07	0.34	0.30-1.65
17	18	7.89	0.17	7.61-8.18	17	0.86	0.41	0.40-2.07
18-21	17	7.85	0.12	7.64-8.07	17	1.22	0.76	0.50-3.61
All	110	7.88	0.18	7.35-8.28	103	1.01	0.46	0.20-3.61
Girls								
12	12	7.95	0.12	7.78-8.18	9	0.73	0.35	0.40-1.47
13	11	7.86	0.15	7.62-8.06	11	0.94	0.59	0.45-2.41
14	28	7.91	0.12	7.63-8.12	24	0.87	0.49	0.35-2.22
15	24	7.94	0.15	7.74-8.22	22	0.92	0.62	0.10-2.24
16	20	7.96	0.17	7.63-8.36	19	1.01	0.67	0.30-2.56
17	19	8.01	0.17	7.70-8.32	18	1.04	0.38	0.40-1.60
18-20	13	7.90	0.16	7.57-8.15	10	0.95	0.29	0.55-1.40
All	127	7.94	0.15	7.62-8.36	113	0.93	0.52	0.10-2.56

SUMMARY

Studies were made on the blood of 110 boys ranging in age from 12 to 21 years and of 130 girls ranging in age from 12 to 20 years who had been chosen as 4-H Club health champions for their respective counties in Minnesota.

For the boys, the mean hemoglobin values increased from 13.0±0.71 gm. per 100 ml. of blood in the 12-year-old group to 15.1±0.76 gm. in the 16-year-olds. Red blood cell counts increased from 4,240,000 ±210,000/cu. mm. to 4,850,000±360,000 during this period. Mean corpuscular hemoglobin showed no significant variation with age, the mean value for the entire group being 30.8±1.12μγ. Red cell diameter also was uninfluenced by the age of the subjects. The observed mean diameter was 7.88±0.18μ. Reticulocyte percentage for the group was 1.01±0.46.

The mean hemoglobin level for the 12-year-old girls was identical with that of the boys in this age group. Thereafter there was a sharp divergence between the sexes, with the levels for the boys increasing and those for the girls remaining essentially unchanged or decreasing slightly. The low point, 12.7±0.81 gm., was recorded for the 16-year-old group, with recovery to 13.3±0.48 gm. in the 18-to-20-year-old group. Red cell counts followed the hemoglobin values, ranging from 4,310,000±170,000 in the 12-year-old group to 4,190,000±270,000 in the 16-year-old group, with recovery to 4,340,000±200,000 in the 18-to-20-year-olds.

Mean corpuscular hemoglobin for the girls, like that of the boys, was uninfluenced by the age of the subjects. The mean for the group was 30.4±1.01μγ. Red cell diameter also showed no significant variation with age; the mean for the girls was 7.94±0.15μ. The reticulocyte percentage was 0.93±0.52.

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The Relationship of Skin pH Pattern to Sexual Maturation in Boys

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The surface of the healthy skin in adults is not uniformly acid. Some zones have a higher acidity than others, and in a few areas where surfaces are in apposition (intertriginous, interdigital, axillary spaces) the reaction may approach neutrality or even alkalinity.*

The presence of these nonacid zones within the physiologic "acid mantle" of the skin has recently become of pediatric interest. Herrmann, Behrendt, and Karp [8] observed in the course of dermatologic investigations that the skin pH pattern in children differs from that of adults mainly by the absence of the "alkaline" reaction in the axillary pits. During childhood, up to about 10 years, the axillary skin pH was found to be more or less acid; but in the older age groups it rose progressively towards the neutral or alkaline values commonly encountered in adults. This increment of pH was regarded as a sign of beginning adolescence, indicating development and activity of the apocrine sweat glands. These glands are predominant in the arm pits, and their secretions are known to be less acid than eccrine sweat (see below). Arbenz [9] confirmed the findings of Herrmann and his associates and accepted their interpretation.

No attempts have been made thus far to relate the shift in axillary pH directly to sexual maturation. Only morphologic changes demonstrating such a relationship are known. Greulich [10] examined histologically samples of axillary skin from more than a hundred children after death and found that the apocrine glands begin to enlarge shortly before "puberty" and do not attain their full development until adolescence is well advanced.

We proposed to study the relationship of skin pH patterns to physical and sexual development in man from birth to senility. The present communication deals with the axillary pH pattern and its relationship to sexual maturation in boys.

It is helpful to review quickly basic data on the apocrine and eccrine sweat glands.

Anatomically, the apocrine glands (a-glands) differ from the eccrine or merocrine sweat glands (e-glands) in the following respects.† A-glands are associated with hair follicles, the glandular ducts opening into the upper portion of the follicles through which the sweat passes along the hair to the surface of the skin. The ducts of e-glands, on the other hand, lead directly through the epidermis to separate openings at the surface of the stratum corneum. A-glands are not only larger than e-glands but are assembled more or less in aggregates. In man these are restricted to certain areas: axilla ("axillary organ"); anogenital region (labia majora, groin, mons pubis, linea alba, peri-

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* References 1, 2, 4, 6, and 7.

† References 11-14.

anal region); mammary areola; ciliary bodies (Moll's glands); external auditory canal.

The manner in which sweat is produced also differs in the two types of glands. In a-glands the distal portion of the secretory cells breaks up so that a portion of the epithelial cytoplasm is delivered along with the secretion. Apocrine sweat is milky and odoriferous, drying like glue to form a light-colored, plastic layer on the skin surface. It may be fluorescent under Wood's light.[15] Eccrine sweat is free of cellular disintegration; it passes from the acini into the ducts and emerges on the skin surface as a colorless liquid.

As to chemical composition, most of the constituents are found in both types of sweat. Little is known about differences in their concentration, e. g., of organic acids.‡ The presence of iron and a high content of cholesterol are probably characteristics of apocrine sweat.§ The outstanding difference concerns the pH. Apocrine sweat and its residue on the skin are considerably less acid than eccrine sweat when tested on the skin.‖ The pH values of the latter are known to range below 5.0-6.0, while the pH of apocrine sweat is found to be one to two units higher. Whether these figures have to be revised for fresh sweat collected from the glands is still a matter of discussion.[21]

The innervation of eccrine glands is cholinergic. Apocrine glands respond to epinephrine or perhaps to both kinds of autonomous stimuli.¶

Little has been established concerning the hormonal control of apocrine function.[24] This represents a field for further study.

SUBJECTS TESTED AND METHODS OF EXAMINATION

A series of 502 boys ranging in age from 4 weeks to 24 years were studied. The distribution according to race and sexual maturity is shown in Table 1. The majority of the older boys, 13 years of age and over, were at the New York State Training School for Boys, in Orange County. The remainder were selected from hospital wards and private practice. They were healthy subjects or were convalescing from an illness. All were afebrile when tested, and their illness, if any, had no known conceivable effect on the activity of the sweat glands. No person with any sort of skin rash was used. None of the boys had any known endocrine disorder.

TABLE 1.—*Composition of the Present Test Series*

	Number of Boys								
					Maturity Group				
Source	White	Negro	Puerto Rican	Total	I	II	III	IV	V
Hospital and practice	93	70	50	213	94	61	23	31	4
N. Y. Training School	109	132	48	289	9	53	93	101	33
Totals	202	202	98	502	103	114	116	132	37

Skin pH Test.—The colorimetric method of Bernstein and Herrmann[6] was employed, with a special modification of the indicator.# An earlier report[8] has dealt with the question of whether this method is as accurate as electrometric pH determinations.[3] Although the absolute pH figures obtained by means of electrodes are more accurate, the consistency of the readings with the indicator have proved satisfactory. In comparative studies such as this one, when estimations to within 0.5 pH unit are adequate, the colorimetric method is reliable and practical.

Test subjects were not allowed to wash the skin for six hours before the test. One drop of indicator was dropped from a pipette or dropper on the site chosen, stirred briefly with a glass rod, and taken up in a perfectly clean glass capillary tube (1 in. long and 0.5 mm. in diameter). The liquid in the tube was then matched in color on the wide-range color chart and the correspondent pH value noted by two observers. Only clear samples were used, all cloudy or dirty specimens being discarded.

‡ References 16-18.

§ References 12 and 19.

‖ References 1-7, 9, and 20.

¶ References 22 and 23.

Modified Universal Wide Range Indicator (Harleco), Standard Scientific Supply Corporation, 34 West 4th St., New York 12.

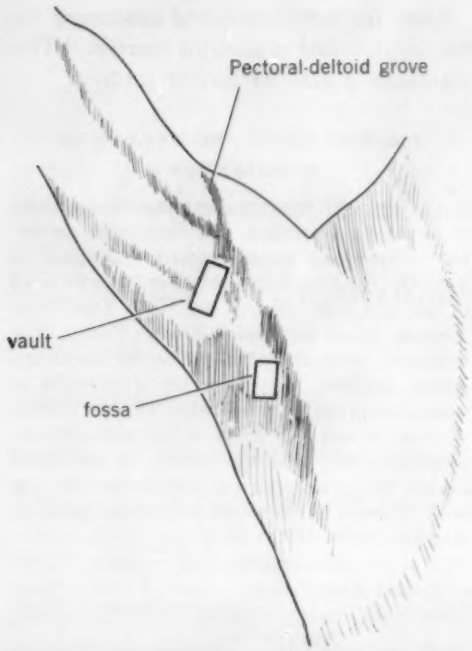

Fig. 1.—Diagram showing the location of axillary vault and fossa and the desired sites for testing the skin pH in these areas.

Since the source and intensity of illumination influence the shade of color in the capillary tubes, readings were done under uniform conditions of light. The test was carried out within 30 seconds. Standardization of this technique is one of the main requisites for accuracy of results.

Areas Tested.—In each subject at each session, the following three sites were tested: axillary vault, axillary fossa, and shoulder region.*

1. Axillary Vault: This site is well within the area overlying the axillary apocrine organ. The region is best exposed when the subject lies on the examination table, places his right palm under his head and rotates his whole body to the left until the right axilla faces upward. In this position, the depression

* In a small number of boys the two axillary sites only were tested (Table 2).

Fig. 2.—Photographs of the axillary space of four boys, illustrating the surface anatomy of vault and fossa as described in the text.

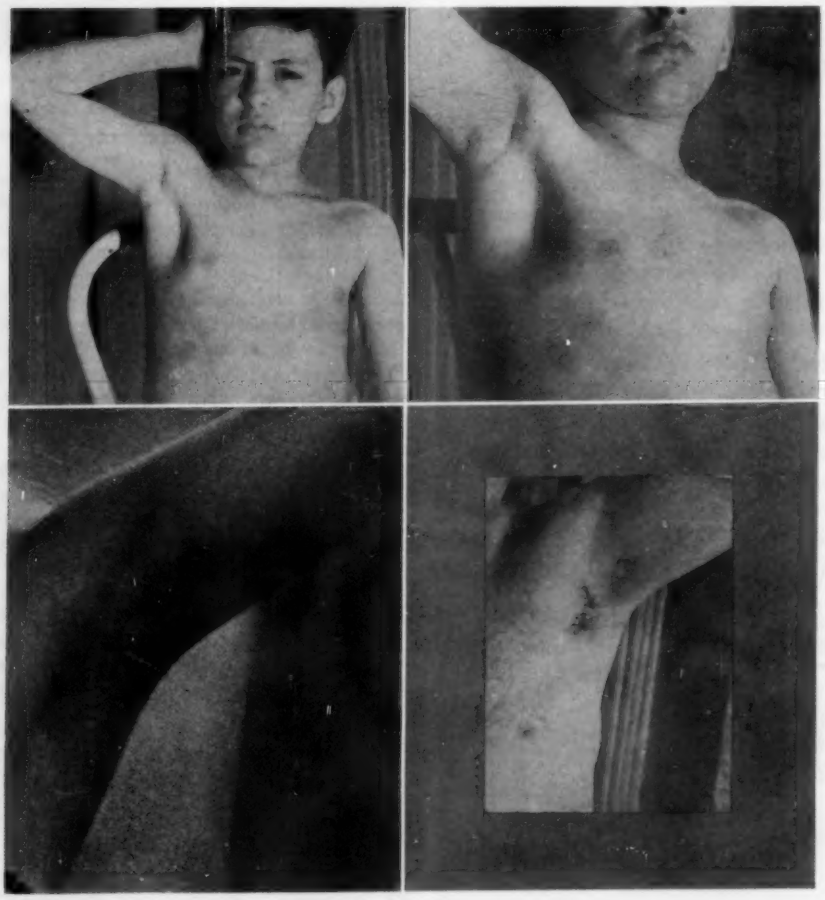

TABLE 2.—*Distribution of pH Readings by Maturity Rate and Skin Region*

Maturity Group	Skin Area Tested	Boys Tested, No.	Number of Boys in Each pH Range							
			2-2.9	3-3.9	4-4.9	5-5.9	6-6.9	7-7.9	8-8.9	9-9.9
I	Ax. vault	103	0	9	73	18	3	0	0	0
	Ax. fossa	103	0	20	71	11	1	0	0	0
	Shoulder	89	10	42	33	4	0	0	0	0
II	Ax. vault	114	0	6	28	26	35	18	1	0
	Ax. fossa	114	2	14	75	16	6	1	0	0
	Shoulder	96	9	33	44	10	0	0	0	0
III	Ax. vault	116	0	0	4	14	48	35	15	0
	Ax. fossa	116	0	6	57	30	17	6	0	0
	Shoulder	109	5	25	59	20	0	0	0	0
IV	Ax. vault	122	0	0	1	2	22	60	47	0
	Ax. fossa	132	0	10	65	35	19	4	1	0
	Shoulder	129	10	34	66	19	0	0	0	0
V	Ax. vault	37	0	0	0	0	6	15	13	3
	Ax. fossa	37	0	2	14	13	7	1	0	0
	Shoulder	37	0	10	25	2	0	0	0	0

TABLE 3.—*Mean Values of Skin pH by Maturity Rates (Three Test Areas, 502 Boys)*

Site	Skin pH in Each Maturity Group				
	I	II	III	IV	V
Axillary vault					
Mean	4.6	5.7	6.6	7.6	7.9
S. D.	0.56	1.15	0.93	0.69	0.71
Axillary fossa					
Mean	4.4	4.6	5.1	5.1	5.3
S. D.	0.56	0.73	0.89	0.93	0.93
Shoulder					
Mean	3.8	4.0	4.3	4.2	4.2
S. D.	0.7	0.76	0.69	0.82	0.48

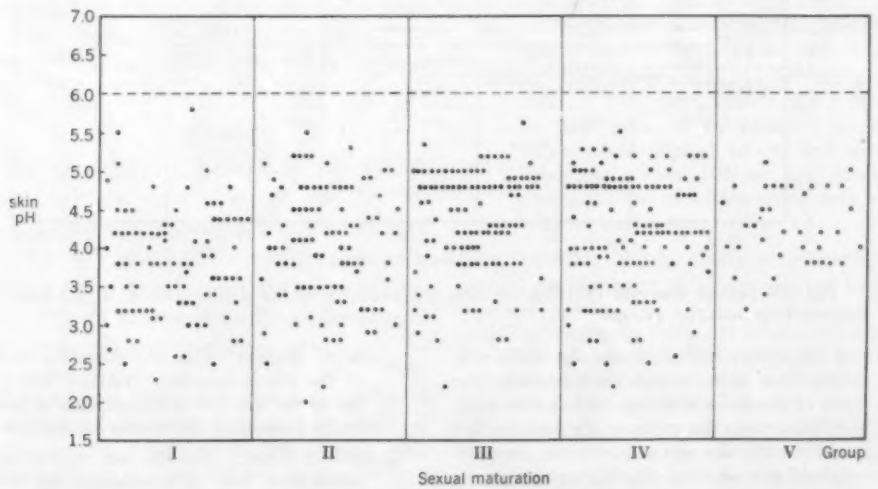

Fig. 3.—Scatter diagram showing the skin pH readings in the shoulder region of 460 boys, arranged by maturity groups.

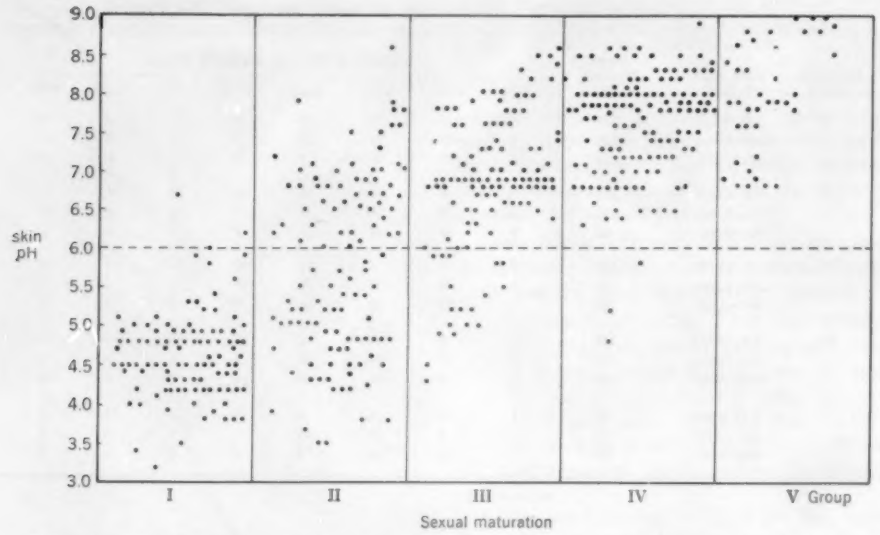

Fig. 4.—Scatter diagram showing the skin pH readings in the axillary vault of 502 boys, arranged by maturity groups.

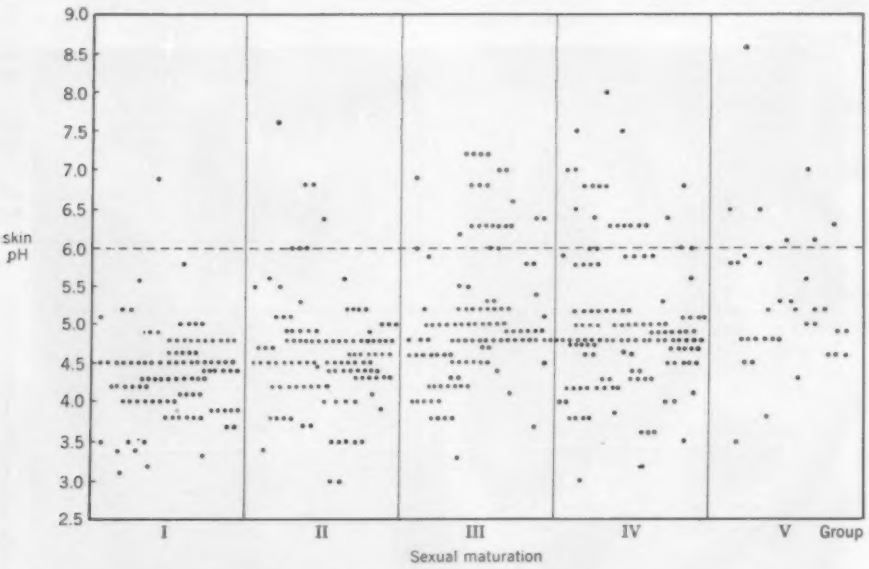

Fig. 5.—Scatter diagram showing the skin pH readings in the axillary fossa of 502 boys, arranged by maturity groups.

of the armpit is shallow and the axilla presents itself as an almost plane surface. The site of choice for applying the test fluid within this area is the center of the axillary fold which continues upward into the pectoral-deltoid groove (Fig. 1). This place corresponds in the upright position to the apex of the vault when the arm is raised at an angle of 45 degrees (Fig. 2). Accurate location of the site is essential. Axillary hair is no bar to the test, but in the presence of profuse axillary sweating the results are not reliable.

2. Axillary Fossa: This site was selected on the assumption that it represented an eccrine area outside the vault but still a part of the axillary space. The anterior border is the

lateral edge of the lower portion of the pectoralis major; the posterior one, the edge of the latissimus dorsi. The changing depth and width of the fossa are noteworthy; its site is illustrated in Figures 1 and 2.

3. Shoulder Region: This is an exclusively eccrine area; it is tested where the deltoid covers the acromion.

Assessment of Sexual Maturation.—In addition to the chronological age, weight, and height, the sexual maturation of each boy was noted according to Greulich's method.[24] The external characteristics which serve as criteria for the five groups of maturity are as follows:

Group I: penis, testes, scrotum of infantile size; no evidence of secondary sex characteristics.

Group II: convincing evidence of active growth of penis, testes, and scrotum; presence of pubic hair.

Group III: further increase in the size of sex organs and in the amount of pubic hair; appearance of facial and axillary hair.

Group IV: amount of pubic hair almost that of adults; size of sex organs increased (corpora cavernosa); facial and axillary hair increased but not yet in adult amounts; acne.

Group V: sex organs have attained adult size; facial, axillary, and pubic hair of adult type; mature body proportions.

Each boy's maturity status is graded in the group to which his status most closely corresponds. We have included in Group II all boys with definite signs of sexual development of any kind, i. e., either active growth of penis and testes or pubic terminal hair, or both. Attempts to further divide this group according to Schonfeld[25] failed to yield uniform results in the hands of different examiners. The terms "puberty" and "adolescence" are used here as defined by Schonfeld.[20] †

RESULTS

The accompanying tables and illustrations summarize the data collected on the 502 boys. Figures 3, 4, and 5 are scattergrams of 1464 individual pH readings. The distribution of pH values in the shoulder region (Fig. 3) is representative of the normal skin acidity in purely eccrine areas. All the values are acid ‡; only a small number are above pH 5.0, and none is above pH 5.8. In contrast, the pH readings in the axillary vault, a predominantly apocrine area, reveal a continous and significant shift toward neutral and alkaline values with each successive maturity group (Fig. 4). In the axillary fossa, where sweat glands are of eccrine type, no characteristic pH shifts are discernible from one group to another.

Table 3 shows the mean pH values as calculated for each maturity group and each area tested. Only the mean pH on the surface of the axillary vault rises steadily through the successive periods of maturation; in the shoulder region, it remains practically constant in all five groups; increases in the axillary fossa are insignificant. The dispersion of values about the mean value within each of the five groups deserves attention: the standard deviation is small in Groups I and V, but it is considerably greater in Groups II, III, and IV.

COMMENT

Under the above conditions of measurement the colorimetric readings obtained on the axillary vault can be classified as follows:

1. Puerile range: pH readings below 5.5, commonly found in infants and children before the onset of apocrine function (eccrine dominance)
2. Maturity range: readings above pH 6.5, which prevail in most adolescents and postadolescents with fully developed apocrine function.
3. Borderline range: readings between pH 5.5 and 6.5. This range extends by 0.5 pH unit on both sides of an assumed borderline between the zones of eccrine and apocrine dominance. These values are frequently obtained in the transition period from childhood to adolescence.§

The sequence of pH changes in relation to sexual development is demonstrated in Fig-

† Adolescence starts with that stage in which the penis and testes begin their spurt of growth in the boy and the breasts in the girl. It ends when full maturity is reached. Puberty is defined as a point when the adolescent boy or girl is capable of procreating.

‡ The few values below pH 3.0 and those above pH 8.5 appear extreme. We have been unable to determine the technical factors which may have been responsible for these readings.

§ It can be anticipated that with different methods of pH measurement the three ranges may be shifted upward or downward on the pH scale. However, their relationship will be always preserved.

ure 6. The established pH patterns have physiologic and clinical implications.

The gradual conversion of the axillary vault pH from acid to neutral or alkaline reaction is an attribute of the activation of aprocrine sweat glands, which, in turn, is a function of reproductive maturation. This may be similar to such other physiological phenomena of sexual maturation as the reversal of vaginal pH from alkaline to acid,[27] the appearance of acid phosphatase activity in the prostate,[28] and the increased urinary excretion of steroids and gonadotropins.[27] The hormonal control of apocrine function has still to be ascertained.[24]

The pH of a given skin area depends not only on the composition of the particular sweat but on the extrinsic factors of evaporation and stagnation. Where skin surfaces are in apposition, there are the acid-antagonizing processes of impaired evaporation and stagnation: acids fail to concentrate, ammonia may accumulate, and excessive keratin hydration may take place. Apparently, the observed changes in the axillary pH pattern during sexual maturation result from the combined effect of these factors and the changing composition of the axillary sweat. In sequence, these changes can be described as follows:

Throughout childhood, the entire axillary region is supplied exclusively with eccrine, "acid" sweat. Stagnation is the sole alkalinizing factor that may produce slightly higher

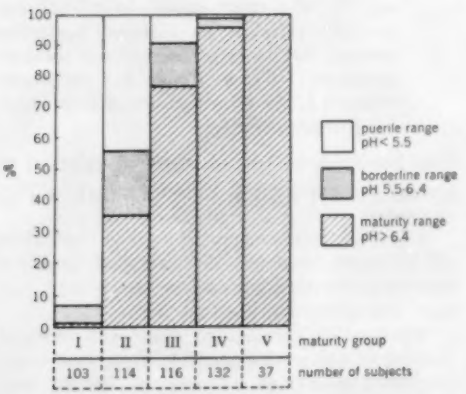

Fig. 6.—Percentage distribution of pH readings on axillary vault by maturity groups (502 boys).

TABLE 4.—*Influence of Race upon Axillary Vault pH*

Race	Mean Vault pH in Maturity Group				
	I	II	III	IV	V
White	4.59	5.80	6.77	7.57	7.84
Negro	4.83	6.01	7.24	7.60	8.03
Puerto Rican	4.52	5.19	6.44	7.48	7.78

pH values than those found in "exposed" eccrine skin areas. As maturity approaches, the apocrine glands and their "alkaline" sweat change the pH pattern. Since a-glands are restricted to the axillary vault, it is this area where the pH is converted from acid to neutral or alkaline values. The peripheral parts of the armpit, including the fossa, do not participate in this apocrine increment of pH. Occasionally found alkaline readings in the fossa may be caused by the admixture of apocrine sweat from the adjacent vault.

Racial differences in the onset and intensity of apocrine conversion of the vault pH were found to be only slight. This corroborates previously reported observations.‖

As a diagnostic test, the determination of the skin pH on the axillary vault reveals the absence or presence of apocrine function, which depends on sexual maturation. In the individual boy, it cannot be used alone as an index of normal or abnormal progress of his development. Wide variations in the time of appearance is a common attribute of all manifestations of maturation. Some boys have an abundance of axillary hair and yet no apparent activity of the a-glands. Contrariwise, pH values in the maturity range may be found in boys without any sign of axillary hair growth. Evidence of active growth of primary sex organs may be present in adolescents unrelated to the pH values found on the axillary vault. The conversion of vault pH does coincide most frequently with the attainment of rich axillary hair growth. The change in axillary vault pH is an additional characteristic of maturation.

SUMMARY

The relationship of skin pH pattern to sexual maturation was studied in 502 boys from 4 weeks to 24 years of age.

‖ References 29 and 30.

There is a progressive rise of the skin pH on the axillary vault from acid to neutral or alkaline values during the period of adolescence.

This conversion of the skin reaction is due to the activation of the apocrine sweat glands as a function of sexual maturation.

Determination of the axillary vault pH may be used as an additional aid in evaluating sexual maturation.

Dr. I. Jay Brightman, Assistant Commissioner for Welfare Medical Services, Department of Social Welfare, State of New York, allowed examinations to be made on students at the New York State Training School for Boys, Orange County. Mr. Alfred Cohn, Superintendent of the New York Training School for Boys, and his staff cooperated in carrying out the studies at that institution. Dr. F. Herrmann gave criticism, and Dr. H. Reed participated in these studies during their early phase.

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Hashimoto's Disease in Childhood

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and
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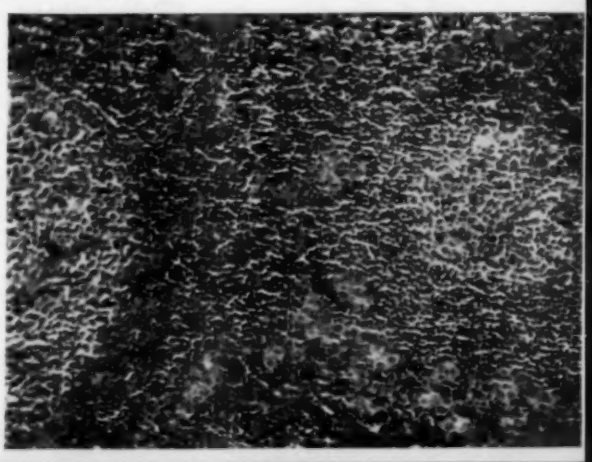
Hashimoto's struma, or struma lymphomatosa, is considered to be a disease of the fifth and sixth decades, but it nevertheless can occur over a wide range of age. In their excellent review of the material from the Massachusetts General Hospital, Statland, Wasserman, and Vickery [1] reported 51 cases between the ages of 10 and 74 years. All were females. Two of their cases occurred at the age of 10 years, one at the age of 14 years; a fourth patient, who had a goiter since the age of 12, was diagnosed as having Hashimoto's struma at the age of 21. Gribetz, Talbot, and Crawford added three additional adolescent cases in 1954 and collected 11 others from the literature.[2] Standard textbooks rarely refer to the possibility of this disease in childhood. It is probable, however, that the incidence in the pediatric age group is higher than generally conceded.

REPORT OF A CASE

The patient, an 11-year-old white girl, was admitted to the hospital on Nov. 30, 1953. According to her mother, a lump had first been noticed in the child's neck on June 7, 1950, and she was taken to a nearby hospital in Nuremburg, Germany, for evaluation. The physicians started her on a strong iodine solution, U. S. P. (Lugol's solution), 1 drop 3 times daily, in view of the local iodine-deficient water. There had been no history of weight loss, increased appetite, nervousness, intolerance to heat, or other sign of hyperthyroidism. Basal metabolic rates were within normal limits. In September, 1952, the family moved to Augusta, Ga., where a slight further enlargement of the thyroid gland had been noted by the mother. The child was treated by the Medical Service on an outpatient basis in April, 1953, at which time her basal metabolic rate was minus 24; a protein-bound iodine was 2.8γ per 100 cc.; cholesterol, 344 mg. per 100 cc.; RBC, 4,800,000; WBC, 6,400; neutrophiles, 47%; lymphocytes, 50%; monocytes, 2%; eosinophiles, 1%; normal urinalysis. The skin was noted to be rather coarse and dry. The blood pressure was 86/40 and the pulse 80. The patient was given ¼ grain (16.3 mg.) of thyroid per day followed by gradual increases during the next few months from ¼ to ½ (32.5 mg.) and finally to 2 grains (130 mg.) of thyroid daily. This produced no apparent change in the size of the gland. In July, 1953, the patient had her first menstrual period. Subsequently, basal metabolic rates rose to the euthyroid range.

In November, 1953, surgery was advised because the gland had not decreased in size and because there was apparent nodular change of the right lower pole of the thyroid gland with slight tracheal compression to x-ray studies. Malignant change could not be excluded. Physical examination at the time of admission revealed her height to be 58 in., her weight, 102 lb. The eyes, ears, nose, and throat were normal, and there were no palpable cervical lymph nodes. The thyroid was diffusely enlarged, with a 1 cm. nodule at the right lower pole. The breasts were enlarged and symmetrical. The lungs were clear. The heart was normal. The abdomen was normal, with pubic hair. The labia showed moderate development. The extremities were normal. Rectal examination was normal. Repeated laboratory studies all reflected a euthyroid state. On Dec. 3, 1953, the patient was operated on, and a frozen section showed Hashimoto's disease. Approximately one-half of the right and left thyroid lobes were removed. The thyroid was grossly enlarged bilaterally, with nodularity at the right

Fig. 1.—Swollen, atrophic, acinar cells are seen between lymphoid follicles; reduced approximately ¼ from mag. × 175.



U. S. Army Hospital, Camp Gordon, Ga.

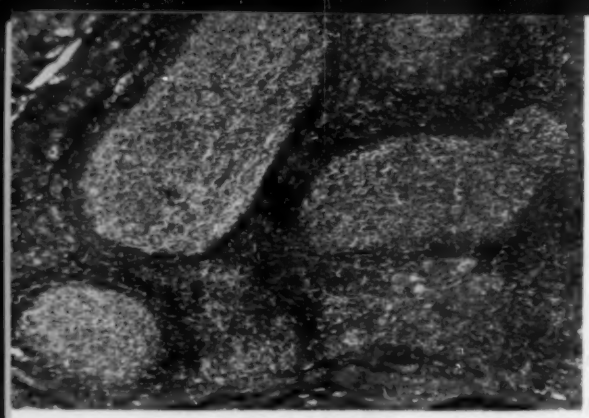


Fig. 2.—Lymphoid follicles with prominent germinal centers are present throughout the thyroid gland; reduced approximately ¼ from mag. × 50.

lower pole. The capsule was clear of any adherence to surrounding structures. The pathologic report of the resected specimen showed the capsule to be smooth and glistening, with a pinkish-gray color to the gland. The under surface of the specimen was irregular, with a homogenous grayish-brown appearance. Tissue was rubbery and homogenous. No circumscribed nodules could be demonstrated. The resected portions of the gland weighed 18.5 gm. Definitive microscopic sections were reviewed at the hospital at the Third Army Pathologic Center and by regional consultants to confirm the diagnosis of struma lymphomatosa (Hashimoto's disease).

The patient continued to require prolonged therapy with thyroid. In June, 1954, her BMR was —34, her weight 115 lb. Recurrence af the thyroid enlargement has not been noted to date.

COMMENT

Hashimoto's disease has only occasionally been reported under 30 years of age.* In children the diagnosis must be entertained with caution and only when careful review of the clinical and pathological features of the case are suggestive. The microscopic picture alone is neither conclusive nor specific, as the characteristic lymphoid follicle infiltration may be seen in patients with Graves' disease, adenomatous goiter, occasionally in colloid goiter, Reidel's struma, and the atrophic thyroid of primary myxedema.[1] Polymorphonuclear cells, plasma cells, and giant cells should not be seen in sections of Hashimoto's struma. The characteristic oxyphilic atrophy of the glands, with scanty colloid formation and occasional foci of hyperplastic acini are generally present; however, they must be further interpreted in light of drug therapy. These changes are diffuse and involve both lobes of the thyroid gland. The patient is almost always a female. The history should reveal gradual enlargement of the thyroid gland over a period of several years without any tendency or suggestion of hyperthyroidism. Most of the patients will be euthyroid, but some with more advanced change will be myxedematous. A goiter and symptoms of pressure or discomfort in the neck are not specific for Hashimoto's struma. Tenderness, if present, is suggestive of some other thyroiditis.

Conservative management of struma lymphomatosa is generally agreed upon when the diagnosis is certain.[2] These patients rarely respond to iodine therapy and are usually supported with thyroid. In many instances the thyroid enlargement will decrease in size with the thyroid hormone supplement.[1] Radiation with 1200r has brought about a dramatic decrease in the size of the gland also.[1] Occasionally, when there is nodular change or persistence of the gland with compression symptoms, surgical interference must be considered. The operative procedure should first be directed toward obtaining the correct diagnosis and second toward relieving local pressure on the trachea. There would appear to be little advantage in removing more tissue after accomplishing these purposes. Radical resection of the gland will only result in earlier signs of myxedema.

Postoperative care will usually require continued thyroid supplement and frequent follow-up examinations. In many instances reoperation has been required for compression symptoms; however, increased doses of thyroid and radiation may give relief.

Excellent summaries of the theoretical etiological factors in Hashimoto's disease are available.† The female sex distribution, the usual incidence during the menopause, and now the several cases at the age of puberty would, in our opinion, lend weight to an endocrine stress theory.

1242 du Pont Building, Miami, Fla. (Dr. Davis).

* References 1 and 2.

† References 4-6.

The Department of Pathology, University of Georgia School of Medicine; the Department of Pathology, University of Miami School of Medicine; the Department of Pathology, Veterans Administration Hospital, August, Ga., and the Third Army Pathology Laboratories provided reviews of the pathologic material.

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CORRECTION

In the article "Chronic Moniliasis Associated with Addison's Disease," by Drs. John M. Craig, Lester H. Schiff, and James E. Boone, in the June issue of this Journal, the legends for Figures 11 and 12 (p. 679) are interchanged. Figure 11 is a photomicrograph of a section from the adrenal; Figure 12, of a section from one parathyroid gland. Corresponding changes should be made in the text references to these Figures.

Congenital Mitral Atresia with Hypoplastic Nonfunctioning Left Heart

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Congenital hypoplasia of the left heart is characterized pathologically by the presence of a diminutive left atrium and a markedly hypoplastic, nonfunctioning left ventricle. This failure in development of cardiac chambers is uniformly associated with an obstructing deformity, either atresia or severe stenosis, at one or both of the valvular orifices on the left side of the heart. The variability of the valve areas involved provides a convenient basis for a simple classification of these malformations into three distinct pathologic groups. The first of these consists of those instances of hypoplasia of the left heart in which the aortic valve is atretic or sufficiently stenosed to prevent the egress of more than a minute amount of blood through this orifice. The mitral valve in this group is perfectly formed but diminutive. The second variety includes those cases in which the mitral valve is the major site of obstruction, while the aortic valve is normally formed but may be smaller than usual. The third group is made up of those cases showing gross deformity with obstruction to blood flow at both the aortic and mitral valve areas. The case reports which are presented in this paper provide examples of the latter two groups, the first variety (aortic atresia with nonfunctioning left ventricle) having been considered by the authors in a previous communication.[1] Aortic or mitral atresia associated with complete transposition of the great vessels or the presence of a common truncus arteriosus will be omitted from consideration here, since these complicating anomalies involve fundamentally different embryologic and physiologic aberrations.

Applying the above classification to a review of the literature, it is possible to determine the relative incidence of the various pathologic types of this cardiac malformation, despite the gross confusion which exists as a result of a lack of uniform nomenclature. Combined aortic and mitral atresia occurs most commonly. Almost as frequently encountered are instances of primary aortic atresia, while isolated mitral atresia of congenital origin occurs least commonly and may, indeed, be considered a rarity. Only nine case reports fulfilling the criteria for hypoplasia of the left heart with atresia of the mitral valve alone were discovered.* These are listed in the Table. Forty-one examples of primary aortic atresia have been tabulated previously by the authors. To these may be added two reported cases previously unnoted † and one recently observed by the authors, making a total of 44 cases. Forty-five instances of combined aortic and mitral atresia were gathered from the literature.‡

Extreme hypoplasia of the left ventricle is characteristically present in all cases of mitral and/or aortic atresia. This chamber exists as an endothelial-lined slit-like cavity 1 or 2 cm. in length which is embedded in the superior-posterior portion of the hypertrophied right

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* References 2-9.
† References 10 and 11.
‡ References 9 and 12-44.

*Data on Eleven Cases of Primary Mitral Atresia with Hypoplasia of the Left Heart**

Author	Age	Sex	Mitral Valve	Foramen Ovale	Ventricular Septum †	Great Vessels	Comment ‡
Donnally [2]	2 days	F	Extreme stenosis	Patent; large	Intact	Rudimentary aorta	.....
Edwards & DuShane [3] (Case 1)	27 days	♀	Atresia	Closed	Multiple small defects in muscular portion of IV septum	Pulm. art. larger than aorta; normal position of aorta	Levoatriocardinal vein; RAD in ECG
Edwards & Rodgers [4]	4 mo.	M	Absent	Patent; 0.6×0.2 cm. in diameter	IVSD; 0.6×0.3 cm. in diameter	Aorta of normal size	Ductus arteriosus closed; RAD in ECG
Friedman, Murphy, & Ash (Case 1)	10 days	F	Atresia	Patent; 0.5 cm. in diameter	IVSD; 0.6 cm. in diameter	Dextroposed aorta	LAD in ECG
Friedman, Murphy, & Ash (Case 2)	4 mo.	M	Atresia	Patent; 0.5×0.1 cm. in diameter	IVSD	Dextroposed aorta	RAD; RVP in precordial leads
Large [5] (Case 1)	14 days	M	Absent	Patent	Subaortic IVSD	Dextroposed aorta	.....
Lawrence & Nabarro [6]	3½ mo.	F	Absent	Patent; 0.5 cm. in diameter	Subaortic IVSD	Overriding aorta	Multiple anomalies of abdominal viscera
Scriba [7]	Stillborn	F	Atresia	Patent foramen primum	Subaortic IVSD	Overriding aorta	One pulmonary vein entering the right atrium
Yost (quoted by Scriba [7])	7 days	F	Atresia	Patent	Subaortic IVSD	Overriding aorta	.....
Spolverein & Barbieri [8] (Case 7)	40 days	M	Absent	Almost completely closed	Subaortic IVSD	Overriding aorta	Ductus arteriosus practically closed
Theremin [9] (Case 106)	2 days	M	Atresia	Closed	Subaortic IVSD	Markedly overriding aorta	.....

* Cases of mitral atresia associated with aortic valve involvement other than simple hypoplasia have been excluded. Patency of the ductus arteriosus was present except where indicated.

† IV indicates interventricular septum; IVSD, interventricular septal defect.

‡ RAD indicates right axis deviation; LAD, left axis deviation; RVP, right ventricular preponderance.

ventricular wall. The cardiac apex is made up of right ventricular musculature. So inconspicuous is the left ventricular chamber that repeated references have been made to the ease with which such a diminutive cavity may be overlooked at postmortem examination. Several instances of aortic and/or mitral atresia have been reported in association with only a single ventricle containing a single tricuspid auriculoventricular orifice. In many of these specimens a primitive, incompletely formed interventricular septum has been described, and this finding has been offered as evidence of failure of development of the interventricular septum. It is our concept that congenital aortic and/or mitral atresia is invariably associated with the presence of two ventricular cavities. In the cases mentioned above, the so-called rudimentary interventricular septum, we believe, is merely the normal separation of the dilated and hypertrophied conus from the main cavity of the hypertrophied right ventricle. Therefore, we have included in our data those cases from the literature in which only a single ventricle with a single auriculoventricular orifice is reported in association with aortic and/or mitral atresia. Cases 3 and 4 in the present series had originally been diagnosed as instances of trilocular heart with a single ventricle. To verify our theory subsequent efforts to find the hidden left ventricle were successful.

In order to maintain postnatal life in the presence of a hypoplastic left heart containing one or more atretic valves, there must be available a patent foramen ovale, or some other anomalous venous passage which permits arterial blood from the left atrium or pulmonary veins to reach the right side of the heart. McIntosh [26] and, more recently, Edwards and DuShane [3] have presented examples of unusual vascular connections between the left atrium and the left innominate vein or superior vena cava associated with mitral atresia and premature closure of the foramen ovale. A similar connection between a left pulmonary vein and the superior vena cava is described in Case 6 of the present series. In a case reported by Scriba,[7] one pulmonary vein emptying into the right atrium served the same purpose.

In patients with mitral atresia or extreme stenosis plus aortic atresia another compensating anomaly essential for survival is a patent ductus arteriosus. This vessel seems to be a continuation of the pulmonary artery and provides the major portion of blood received by the descending aorta plus some retrograde flow to the aortic arch, its branches, and the coronary vessels. The pulmonary artery is larger than normal, often twice or three times the size of the aorta at its base. None of the reported cases of atresia or extreme stenosis of both the mitral and aortic valves associated with a hypoplastic, nonfunctioning left ventricle demonstrated a functioning interventricular septal defect. Taussig's case [15] which was associated with an interventricular septal defect was erroneously included in the previous communication on aortic atresia written by the authors. Reexamination of her data revealed the fact that, although the left ventricle was small, it was of sufficient size to form the left border and apex of the heart. It falls, therefore, into the group of hearts with aortic stenosis and a functioning left ventricle.

When the mitral valve alone is atretic, a high interventricular septal defect is a common finding usually associated with a dextroposed overriding aorta, thus favoring the passage of some blood from the right ventricle into the left ventricle and the first portion of the aortic arch. In these instances, hypoplasia of the ascending aorta is less marked and may be absent. Unless some degree of dextroposition of the aorta exists, the presence of a patent ductus or a defect in the muscular portion of the ventricular septum is mandatory to permit the entrance of blood into the systemic circulation. The cases of Donnally [2] and of Edwards and DuShane [3] were the only instances in which no dextroposition of the aorta was present.

As a result of the primary and secondary malformations mentioned above, the pathway of blood flow in hearts deformed with mitral atresia is grossly abnormal (Fig. 1). Venous blood arriving in the right atrium from the

vena cava passes into the spacious right ventricle and out to the lungs via the dilated pulmonary artery. Here it is oxygenated in the usual fashion and returned to the left atrium through the pulmonary veins. Since little or no blood can pass beyond the left atrium because of the valvular obstruction, the stream of oxygenated blood is diverted through the patent foramen ovale to be mixed with the venous blood of the right atrium. Only mixed venous-arterial blood reaches the systemic circulation either through an overriding aorta or through a patent ductus arteriosus. This highly unsaturated, mixed

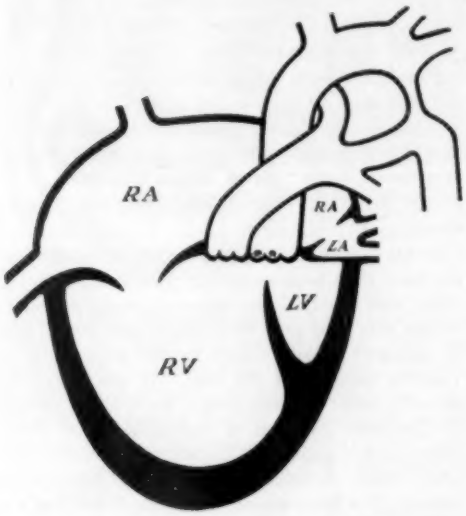

Fig. 1.—Diagram illustrating the usual combination of congenital anomalies found in association with primary mitral atresia and hypoplasia of the left heart. The aorta is seen overriding a defect in the upper portion of the ventricular septum. The pulmonary artery arises from the right ventricle. The ductus arteriosus and foramen ovale are patent. *RA* indicates right artium; *RV*, right ventricle; *LA*, left atrium; *LV*, left ventricle. (Reproduced with permission from Large, H. L., Jr.: *Am. J. M. Sc.* **219**:268-275, 1950, Lea & Febiger, Philadelphia, publisher.)

blood supplies the entire systemic circulation as well as the coronary arteries.

The disadvantages of such a circulatory arrangement are obvious. A double burden is placed upon the right ventricle, which must propel the blood through both the pulmonary and the systemic circulation. Arterial blood as such never reaches the systemic or coronary circulations, since it first is mixed with the venous contents of the right atrium. Thus, the combined deleterious effects of right-sided cardiac failure and severe generalized anoxemia, each complementing the other, lead typically to an early death in these patients.

REPORT OF CASES

CASE 1.—Atresia of mitral valve; hypertrophy and dilatation of right atrium and right ventricle; hypoplasia of left atrium and left ventricle; patent foramen ovale; probe patency of ductus arteriosus; interventricular septal defect; dextroposed aorta; slight coarctation of aorta; anomalous right subclavian artery. Prominent islets of Langerhans in pancreas (history of maternal diabetes).

J. McN., a white girl, aged 10 days at death, was born at home weighing 3300 gm. Her 33-year-old multiparous mother was treated for diabetes mellitus during the final trimester of her pregnancy. The father was 35 years old and in good health. There were two siblings living and well. The patient breathed and cried promptly and was not noted to be cyanotic at birth, although one observer did comment that the infant was not as pink as most newborn infants. The infant appeared well until the eighth day of life, when respiratory distress and cyanosis were first noted. She was admitted to Children's Hospital of Philadelphia on this day. Physical examination revealed grayish cyanosis about the lips, which was relieved by oxygen. There was marked respiratory distress with inspiratory retraction in the region of the xiphoid. Enormous cardiac enlargement was noted on percussion. A prolonged systolic murmur was audible over the entire anterior chest wall, maximum in the region of the third and fourth interspaces to the left of the sternum. The second pulmonic sound was accentuated. The liver was firm and enlarged to the level of the umbilicus. The spleen was not palpable. The patient was placed in an oxygen tent and digitalized, but improvement was only temporary. The course thereafter was marked by increasing respiratory distress and deepening cyanosis, with death occurring two days after admission.

The blood cell count on admission revealed a hemoglobin level of 16.5 gm., with a red blood cell count of 5,750,000. The white blood cell count was 14,700, with 72% neutrophiles and 28% lymphocytes. A blood sugar determination done shortly after admission was 70 mg. per 100 cc. A roentgenogram of the chest (Fig. 2) showed enormous enlargement of the heart both to the right and left of the sternum in the anteroposterior view. In the lateral view, the posterior border of the heart

seemed to be in the normal position, but the anterior surface hugged the chest wall. The electrocardiogram showed diphasic QRS complexes with prominent S waves. The QRS interval was prolonged in Lead II. No precordial leads were taken.

At necropsy the heart weighed 50 gm. The great vessels arose in normal anteroposterior relationship, the aorta being the smaller vessel. The venae cavae terminated normally in a greatly dilated right atrium with thickened musculature and prominent appendage. The valve of the foramen ovale was fenestrated. In addition, there was an uncovered orifice of 0.5 cm. diameter. The right ventricle, which formed the main ventricular mass, was

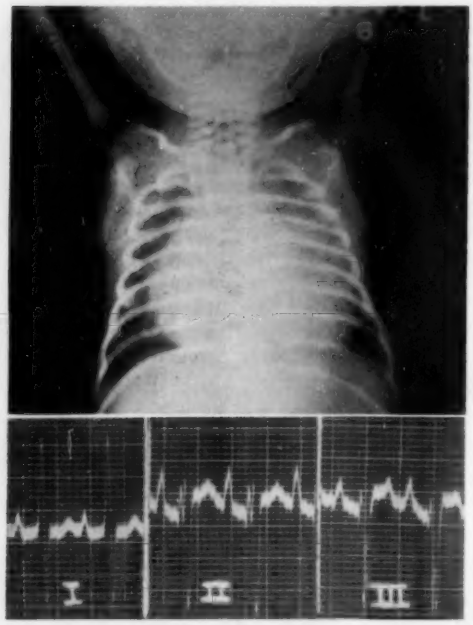

Fig. 2 (Case 1).—The roentgenogram demonstrates massive cardiac enlargement. The electrocardiogram shows marked left axis deviation.

markedly dilated and hypertrophied with a prominent pulmonary conus. The tricuspid and pulmonary valves were normal, measuring, respectively, 5.5 and 2.5 cm. in circumference. Immediately above its origin the pulmonary artery presented a bulbous dilatation 1.0 cm. in diameter. It gave rise to right and left branches in the normal fashion. The ductus arteriosus was patent only to a fine probe. Two pulmonary veins entered the left atrium, which was extremely small, the greatest diameter being 1.0 cm., as compared with 4.5 cm. for the right atrium. The only outlet was the patent foramen ovale. No mitral valve was present. The left ventricle was represented by a small, pear-shaped promontory situated on the upper, posterior aspect of the main ventricular mass and containing a minute endothelial-lined chamber. This ventricular chamber measured 1 × 1 cm. and terminated in a narrow orifice at the upper pole. A ventricular septal defect 0.6 cm. in diameter was situated behind the septal cusp of the tricuspid valve. The aorta was dextroposed so as to arise partly over this defect and partly over the orifice of the rudimentary left ventricle. An aortic valve guarded by normally formed cusps measured 1.5 cm. in circumference. The diameter of the ascending aorta was 0.4 cm. It narrowed progressively, reaching a diameter of 0.2 cm. at the isthmus. The coronary arteries arose in the normal fashion. Two large vessels were given off from the right half of the aortic arch and two from the left half. The most distal vessel originated at the junction of the transverse and descending arch and passed backward behind the esophagus to become the right subclavian artery.

Case 2.—Atresia of mitral valve; hypertrophy and dilatation of right atrium and right ventricle; hypoplasia of left atrium and left ventricle; slightly patent foramen ovale; interventricular septal defect; dextroposed aorta; patent ductus arteriosus; congenital defect of parietal bone; aspiration pneumonia.

R. M., a white boy, aged 4 months at death, was the third child born to healthy parents. Pregnancy, labor, and delivery were uncomplicated; the birth weight was 2730 gm. No cyanosis was noted, and he appeared normal except for the presence of a vascular anomaly of the scalp. At the age of 11 days the infant was admitted to the surgical service of Children's Hospital of Philadelphia for treatment of a hemangioma of the occipital portion of the scalp which communicated with the intracranial sinuses. The hemangioma was excised and the abnormal communicating vessels ligated. The wound healed slowly because of postoperative infection. The infant was discharged at the age of 1½ months weighing 3415 gm. The hemoglobin level at the age of 11 days was 18 gm. Transient attacks of cyanosis had been noted during this admission, but no cardiac studies had been made.

The patient's second and final admission occurred at the age of 4 months. He had seemed to be doing well and had gained up to 4325 gm. Ten days prior to admission he suddenly became cyanotic and dyspneic after a feeding. A pink color returned after a few moments of crying, but from that time on the appetite was poor and feeding difficult. Because of weight loss and the development of a cough the patient was admitted to Children's Hospital of Philadelphia for study. Shortly after admission he suddenly developed marked cyanosis and dyspnea. The lungs seemed clear. The area of cardiac dullness extended to the anterior axillary line. No murmurs

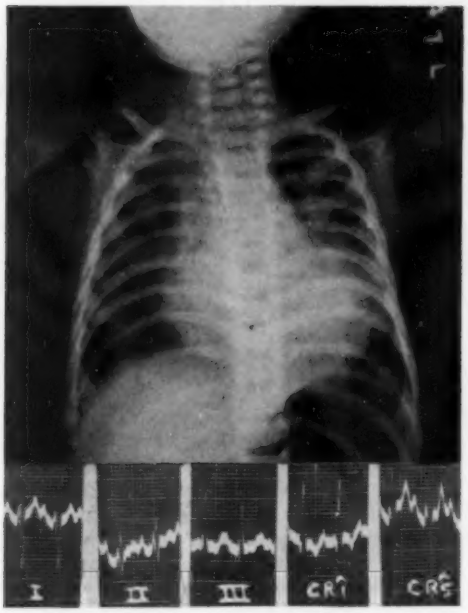

Fig. 3 (Case 2).—The roentgenogram shows moderate cardiac enlargement with prominence in the region of the pulmonary artery. The electrocardiogram demonstrates right axis deviation and right ventricular preponderance.

were audible. The cardiac rhythm was regular and the rate 140. Blood pressure was 110/70. The liver was felt 5 cm. below the right costal margin. Femoral pulses were palpable. The infant was treated with oxygen, digitalis, and morphine sulfate because heart failure was suspected. There was little response to therapy, and he died about 36 hours after entry.

The hemoglobin on this admission was 17.5 gm.; red blood cells, 6,700,000. Roentgenographic examination of the chest (Fig. 3) revealed marked cardiac enlargement to the left in the anteroposterior view. There were increased vascular markings throughout both lung fields together with a small area of pneumonitis in the left lower lung field. The electrocardiogram showed marked right axis deviation in the limb leads and findings indicative of the presence of right ventricular preponderance in the precordial leads.

At necropsy, the head presented a defect of the skull extending anteriorly from the posterior fontanel, measuring 3×2 cm., with a well-healed 4 cm. scar in the scalp over this area. Except for flattening of the gyri under the skull defect, the brain seemed normal. No anomalies were noted in the blood vessels to the head.

The heart was markedly enlarged, composed mainly of a greatly dilated and hypertrophied right atrium and right ventricle. The foramen ovale was almost completely covered by a valve, leaving a narrow opening, 0.5 cm. in length and 0.1 cm. in width. The tricuspid valve, guarded by three normal cusps, was 5.5 cm. in circumference. An interventricular septal defect 0.5 cm. in diameter was situated behind the septal cusp. The pulmonary artery arose in its usual position and gave rise normally to right and left pulmonary branches. The ductus arteriosus was patent, with a diameter of 0.4 cm. The left atrium was very small, its only exit being through the relatively small opening in the foramen ovale. The mitral valve was represented only by a depression 0.5 cm. in diameter covered by a thin membrane. The left ventricle appeared as a small endothelial-lined slit in the upper posterior portion of the ventricular mass immediately below the left atrium. A normal-sized aorta, 1.2 cm. in diameter, arose partly over the interventricular septal defect and partly over the upper orifice of the minute left ventricle. The aorta narrowed progressively to a diameter of 0.6 cm. immediately proximal to the ductus arteriosus. The pulmonary artery was larger than the aorta, the diameter being 1.5 cm. The circumference of the pulmonary valve was 2.6 cm., and of the aortic valve, 2.9 cm.

Case 3.—Aortic and mitral atresia; hypertrophy and dilatation of the right atrium, right ventricle, and pulmonary artery; hypoplasia of the left atrium, left ventricle, and ascending aorta; persistent left superior vena cava; patent ductus arteriosus; aber-

Fig. 4 (Case 3).—Photograph of postmortem specimen in case of combined mitral and aortic atresia associated with hypoplastic left heart demonstrating large right atrium (*RA*) and right ventricle (*RV*) with dilated pulmonary artery (*PA*) conrtasted with hypoplastic first portion of aortic arch.

rant artery of the left kidney; early bronchopneumonia.

Baby D., a white girl, aged 3 days at death, was born in the Harrisburg General Hospital, the first child of a 20-year-old mother. The baby weighed 2915 gm. at birth, cried spontaneously, and seemed normal. Five hours later respiratory difficulty developed. Physical examination was negative except for the presence of an apical systolic murmur. The heart rate was 132. The infant was placed in oxygen. On the following day slight cyanosis was noted; the murmur had increased in intensity, and the rate was 160. There was no improvement following the use of digitalis. At the time of death the infant was deeply cyanotic, and the lower edge of the liver could be palpated 5 cm. below the costal margin.

At necropsy the heart did not seem enlarged. The right superior and inferior venae cavae entered the right atrium in the usual fashion. No innominate vein was present. A left superior vena cava joined the azygous vein and then traversed the posterior wall of a small left atrium to enter the coronary sinus, which was greatly enlarged. The right atrium was markedly dilated. The hypertrophied, dilated right ventricle formed the major portion of the ventricular mass. A dilated pulmonary artery (diameter 1.0 cm.) divided into the usual right and left branches and continued through a large patent ductus (diameter 0.5 cm.) into the descending aorta. The pulmonary veins entered a diminutive left atrium, where the only exit was through an opening in the foramen ovale no greater than the head of a pin. There was no mitral valve. The left ventricle was represented by a minute endothelial-lined slit within the posterior superior portion of the wall of the main ventricle. It presented no exit. The minute aortic orifice was closed by a thin membrane. The ascending aorta was hypoplastic (diameter 0.2 cm.). Below the entrance of the ductus arteriosus the descending aorta had widened to a diameter of 0.4 cm. The coronary arteries and branches of the aortic arch arose in the usual fashion. The circumference of the pulmonary valve was 2.5 cm., and the tricuspid valve, 4.8 cm.

Case 4 (Previously Reported [45]).—Aortic and mitral stenosis; hypertrophy and dilatation of right atrium, right ventricle, and pulmonary artery; hypoplasia of left atrium, left ventricle, and aorta; patent foramen ovale; probe patency of ductus arteriosus; bicuspid pulmonary valve.

J. L., a white girl, aged 5 months at death, was born of a 32-year-old father and a 29-year-old mother, the product of a fourth pregnancy. Two older siblings were living and well. The third pregnancy had ended in miscarriage. The infant was born at term, weighing 3185 gm. Transient attacks of cyanosis were first noted at the age of 4 weeks. When first seen in the Outpatient Department of Children's Hospital of Philadelphia, at the age of 3 months, cyanosis of moderate degree had become constant. A systolic murmur was audible throughout the left chest, maximum at the left border of the sternum. She was admitted at the age of 5 months because of failure to gain weight. The weight was 3870 gm. Deep cyanosis was present. A systolic murmur was heard best at the pulmonary area. The second sound at the pulmonary area was accentuated. A roentgenogram of the chest revealed a globular cardiac shadow markedly enlarged to the left of the sternum, with a lesser degree of enlargement to the right. No electrocardiogram was taken. The red blood cell count was 5,150,000; hemoglobin, 96%. The infant died on the third day following admission.

At the time of writing this paper, the heart was not available for examination. The following findings were reported in the original necropsy record: The right atrium and right ventricle were dilated and hypertrophied, as was the pulmonary artery. The foramen ovale was patent, measuring 1.5 by 0.7 cm. The lumen of the ductus arteriosus was very small. A bicuspid pulmonary valve was present. The left atrium and left ventricle were rudimentary and partly collapsed, containing no blood. The aortic and mitral valves were rudimentary. The circumference of the mitral valve was 2.0 cm.; aortic valve, 1.0 cm.; tricuspid valve, 6.5 cm.; pulmonary valve, 4.0 cm. The circumference of the pulmonary artery was 3.2 cm., and of the ascending aorta, 1.5 cm.

Case 5.—Aortic and mitral stenosis; hypertrophy and dilatation of the right atrium, right ventricle, and pulmonary artery; hypoplasia of the left atrium, left ventricle, and aortic arch; patent foramen ovale; patent ductus; bicuspid pulmonary valve; anomalous pulmonary vein arising from superior vena cava (?); rectovaginal fistula; coloboma of right choroid; atelectasis of lower left and upper right lungs; acute empyema and peritonitis (hemolytic Streptococcus); postoperative anoplasty.

D. Z., a white girl, aged 9 weeks at death, was the fifth child of a 38-year-old father and a 37-year-old mother. The birth weight was 2050 gm. She was admitted at the age of one month because she was losing weight. Examination revealed a marasmic infant of poor color, weighing 2460 gm., with imperforate anus, rectovaginal fistula, coloboma of right eye, and a generalized skin eruption with desquamation of the fingers. No definite heart murmur was noted. After an initial gain in weight, the infant began to decline slowly, vomiting frequently and showing increased cyanosis. Two weeks before death, anoplasty was performed under local anesthesia, following which the child became progressively worse.

On admission the erythrocyte count was 6,120,000, hemoglobin, 106%. Before death the erythrocyte

count was 3,600,000, and the hemoglobin, 72%. The Wassermann test for syphilis was negative for parents and infant. Roentgenograms revealed an enlarged heart of globular contour in the antero-posterior view, with fullness of the pulmonary segment. In the lateral view there was encroachment upon the clear space anteriorly by the cardiac shadow with no enlargement posteriorly. The lung fields showed infiltration throughout, with well-marked density at the right apex. No electrocardiogram was taken.

Only a poorly preserved cardiac specimen was available for our examination. In the original necropsy report there is mentioned an enormously dilated left pulmonary vein stretching over the base of the heart and arising from the superior vena cava. The venous vessels had been cut short in the cardiac specimen, and so we were unable to verify the existence of this anomalous vessel.

The right atrium was tremendously dilated. It opened through a large normally formed tricuspid valve into a dilated right ventricle with hypertrophied walls. The left atrium was very small, about one-fifth the size of the right atrium. The valve of the foramen ovale did not completely cover the opening, leaving an orifice 0.4 by 0.5 cm. in size. A small mitral valve, otherwise well formed, measured 1.0 in circumference. A small left ventricle lying at the upper posterior aspect of the large right ventricle contained only rudimentary papillary muscles. A small aorta arose normally from this chamber and pursued a normal course. The circumference of theaortic valve was 1.2 cm., the valvular leaflets being small but otherwise normal. The interventricular septum was intact. The pulmonary artery was markedly dilated with thickened walls. Its diameter was 1.7 cm. The pulmonary ring was guarded by two competent, normally formed leaflets. The circumference of the pulmonary valve was 2.6 cm. The ductus arteriosus was patent, with a diameter of 0.2 cm. The ascending aorta measured 0.6 cm. in diameter. The coronary arteries and vessels from the arch arose in the usual fashion.

CASE 6.—Aortic and mitral stenosis; hypertrophy and dilatation of right atrium and right ventricle; hypoplasia of left atrium and left ventricle; foramen ovale functionally closed; Meckel's diverticulum.

L. A. M., a white girl, who died at the age of 2½ months, was born in a nursing home to a healthy 31-year-old multiparous mother after an uneventful pregnancy and labor. The father, 38, was also healthy. Of the mother's four pregnancies, the first resulted in a 1365 gm. premature infant who died at the age of 11 hours; the second ended in a spontaneous abortion after two months' gestation; the third resulted in a living, healthy infant, and the fourth, in the patient under discussion. This infant weighed 5035 gm. at birth. She did not breathe spontaneously and was intensely cyanotic. Mouth-to-mouth insufflation was necessary for three and one-half hours, after which time the infant was transferred to a local hospital and placed in an oxygen tent. Oxygen was administered continuously for almost a month, and the diagnosis of cerebral anoxia was offered. On discharge, the infant was still slightly cyanotic, especially about the lips and nails. She also breathed rapidly, had a distended abdomen, and coughed occasionally. Feedings intensified the cyanosis and respiratory distress.

At home the patient failed to gain weight over a period of six weeks. There were recurrent attacks of pallor and sweating. The formula was changed several times because of regurgitation and periodic diarrhea. For a week preceding the terminal illness, she had seemed in improved health.

Three days prior to her admission to Children's Hospital of Philadelphia, she developed an unusual degree of somnolence, with great irritability when awake. On the day of admission, she suffered several severe attacks of cyanosis and passed one grossly bloody stool. On entry, the pulse rate was over 200 per minute and the respiratory rate was 55 per minute. The infant was extremely cyanotic, and breathing was associated with marked costal retractions. Pitting edema of the extremities was noted. The body weight was 4890 gm. The heart sounds were of poor quality, but no definite cardiac murmurs were audible. Cardiac enlargement was apparent. The liver edge was palpable just below the level of the umbilicus. The lungs were free of rales. Femoral and radial pulses were equal and readily palpable. The patient was treated with digitalis, oxygen, and morphine sulfate. After a period of transient improvement, she died suddenly four and one-half hours after admission. Her condition never permitted roentgenographic study. An electrocardiogram showed marked right axis deviation in the limb leads. No precordial leads were taken.

At necropsy, the heart was found to be enlarged, consisting mainly of a greatly dilated right atrium and a hypertrophied and dilated right ventricle. The left atrium was very small. The left ventricle formed a small cavity within the posterior-superior wall of the right ventricle. The aorta and pulmonary artery arose normally from their respective ventricles. The pulmonary artery was large (diameter 1.2 cm.) as compared with the ascending aorta (diameter 0.8 cm.), although the latter was of fair size. The interventricular septum was intact. All valves were normally formed, but the aortic and mitral valves were both small. The following measurements were noted: circumference of tricuspid valve, 6.0 cm.; pulmonary valve, 3.0 cm.; mitral valve, 3.5 cm.; aortic valve, 1.6 cm. The foramen ovale was anatomically open but functionally closed. The ductus arteriosus

was closed. The coronary arteries and vessels from the aortic arch arose in the usual fashion.

A Meckel diverticulum was present proximal to the ileocecal junction. There was no evidence of inflammation or erosion either in this structure or elsewhere in the gastrointestinal tract, and no blood was seen.

COMMENT

The family and obstetrical histories in the six cases of mitral atresia or stenosis presented reveal no consistently significant features. In only one instance was the preceding pregnancy marked by any maternal illness. In Case 1 (J. McN.) the infant's mother was known to have diabetes mellitus, a maternal disease which is recognized to be associated with a high incidence of fetal malformations. The maternal age at the time of delivery varied from 19 to 37 years. None of the infants were of unusual birth weight, the smallest weighing 2050 gm. and the largest 5035 gm. In only the latter infant (L. A. M.) was any difficulty encountered in establishing respiration, and this was thought to be due to central nervous system damage. Four of the six patients were female and two male. In previously reported instances of both varieties of left heart hypoplasia under consideration, no significant difference in sex incidence exists. Major congenital anomalies of other organ systems were present in three of our six patients.

A review of the physical signs and symptoms in this series of six patients with nonfunctioning left ventricle reveals no consistent aids to specific diagnosis. A systolic murmur was audible over the precordium in only three of the six patients. The other three demonstrated no definite murmurs. In none of the three cases in which the observation was recorded were the peripheral pulses reported to be weaker than normal, even though two of these were in patients with associated aortic atresia or stenosis. The classical physical findings of congestive heart failure in infancy were present terminally when death was due to this cause. These included tachycardia, tachypnea, dyspnea, cyanosis, hepatomegaly, cardiomegaly, and gallop rhythm. Clinically detectable evidence of peripheral edema and pulmonary rales was absent in all of our cases except in Case 6, which demonstrated pitting edema of the extremities. In one case death was due to severe bacterial infection, and overt signs of congestive failure were never present. The response to the usual therapeutic measures for congestive failure was uniformly poor.

In the presence of gross admixture of venous and arterial blood in the systemic circulation, it is remarkable that cyanosis was so commonly absent or mild and intermittent until the onset of cardiac failure. While cyanosis was noted prior to the terminal illness in each case, it was frequently not observed for some time following birth. With the onset of cardiac failure, respiratory distress and hepatomegaly became prominent findings. At this time severe cyanosis made its appearance, and a rapid downhill course followed. It has been postulated that the sudden appearance of severe cyanosis with relatively rapid death may be due to a gradually increasing intraluminal pressure within the left atrium, which finally closes the curtain-like valve guarding the foramen ovale and thereby halts the life-preserving left-to-right shunt, cutting off the only source of oxygenated blood to the systemic circulation.

Routine roentgenographic study of the heart revealed gross cardiac enlargement with evidence of right ventricular hypertrophy in all patients examined when the signs and symptoms of congestive failure were present. Massive cardiac enlargement at the time of birth has been offered as a characteristic feature of hypoplasia of the left ventricle.[46] That this finding is not invariably present is demonstrated by an infant with aortic atresia and hypoplasia of the left heart, reported by us in a previous communication, who showed no cardiac enlargement on roentgenograms taken on the first and eighth days of life. Thus we may conclude that, although massive cardiac enlargement may be demonstrable at the time of birth, this is not universally the case. Terminally, demonstrable cardiomegaly of extreme degree is usually present. In such cases prominence of the pulmonary segment

and of the anterior border of the heart in the right antero-oblique view indicate the presence of hypertrophy and dilatation of the right ventricle and pulmonary artery. Other suggestive fluoroscopic findings are those of right auricular enlargement and dilatation of the superior vena cava. The lung fields characteristically show no paucity of vascular markings.

In the first two patients presented, that is, in those with mitral atresia and no aortic atresia accompanying hypoplasia of the left heart, electrocardiograms are available. One of these demonstrated right axis deviation in the limb leads and right ventricular preponderance in the precordial leads. The other tracing, that of Case 1 (J. McN.), reveals marked left axis deviation in the limb leads, a finding that might not be anticipated in the presence of right-sided cardiac hypertrophy. Soloff [21] has reported a somewhat similar phenomenon in a case of combined aortic and mitral atresia with hypoplasia of the left heart and marked hypertrophy of the right ventricle in which the electrocardiogram also demonstrated left axis deviation in the limb leads. His explanation for this apparent paradox is the fact that axis deviation depends upon the electrical position of the heart. Thus when the heart is electrically closer to the left arm than to the left leg, left axis deviation tends to occur in the electrocardiogram regardless of the particular chamber enlarged. In only one of our patients with combined aortic and mitral stenosis was an electrocardiogram recorded, and this demonstrated a marked right axis deviation in the limb leads.

The pathologic findings in our six cases demonstrate some of the basic differences and similarities of the two varieties of hypoplasia of the left heart under consideration. In all instances the left ventricle was extremely small and nonfunctioning. The left atrium was also consistently hypoplastic. Over-all cardiac enlargement was present in all but one instance. In five of the six infants some degree of patency of both the foramen ovale and the ductus arteriosus existed. The single case (L. A. M.) demonstrating complete closure of these structures was one in which stenosis and not atresia of the mitral and aortic valves was present. In the four instances of combined mitral and aortic atresia, the interventricular septum was intact. In contrast, an interventricular septal defect was present in the two infants with isolated mitral atresia. In the presence of aortic valve involvement, hypoplasia of the aortic arch at its base was uniformly observed. In such specimens the diameter of the pulmonary artery was usually two to five times greater than that of the aorta. When only the mitral valve was involved, an interventricular septal defect associated with abnormality in the position of the aorta was seen. In these instances dextroposition of the aorta was present with overriding of the interventricular septal defect. In two of the six cases a bicuspid pulmonary valve was found. In a single instance an anomalous left pulmonary vein arising from the superior vena cava was probably present. Other cardiovascular anomalies encountered were as follows: mild coarctation of the aorta, persistent left superior vena cava, retroesophageal right subclavian artery, and an aberrant left renal artery.

While various pathologic forms of hypoplasia of the left heart may be classified on the basis of the valvular structures involved, the clinical features do not permit identification of these entities prior to death. During life one can make a diagnosis of marked right-sided cardiac hypertrophy with prominence of the pulmonary segment suggestive of accompanying dilatation of the pulmonary artery. By inference the conclusion may be drawn that the left heart is functionally unimportant. Although cyanosis and the early appearance of right-sided cardiac failure are not always obvious at birth, these findings when present may be taken as added indications of the possible presence of hypogenesis of the left heart associated with right ventricular enlargement.

It is theoretically possible that angiocardiography may contribute toward a premortem diagnosis in this group of cardiac anomalies. With combined mitral and aortic atresia, one would expect to observe early and dense

filling of the descending aorta with little or no opacification of the hypoplastic ascending and transverse portions throughout the duration of the study. A large right atrium, right ventricle, and pulmonary artery associated with failure of the left ventricle to opacify at any time might also be anticipated. Refilling of the right heart via an interatrial communication from a diminutive and persistently opacified left atrium might also be observed. In the cases of mitral atresia without aortic atresia, the high ventricular septal defect and dextroposed aorta might permit early visualization of the entire aorta with uniform density. However, some discrepancy in the relative size of the two great vessels might be apparent and together with absence of left ventricular filling might suggest this diagnosis. We have been able to make the premortem diagnosis of hypoplasia of the left heart in a patient with mitral atresia who also showed transposition of the great vessels, both arising from the right ventricle, based mainly on failure of visualization of the left ventricle.

From the practical point of view, differentiation of the various pathologic types of hypoplasia of the left heart remains in the realm of academic interest at the present time, since no surgical procedures applicable to the treatment of this variety of congenital heart disease are available. Creation of an atrial septal defect would produce partial and only temporary relief in these anomalies.

In contrast to the extremely early death suffered by the infants with hypoplasia of the left heart associated with congenital aortic atresia, the survival time of patients with mitral atresia as the primary lesion is somewhat longer. The vast majority of patients with aortic atresia alone died within the first week of life, and only 2 of the 41 tabulated cases survived beyond the first month of life. The same general prognosis holds for the cases of combined aortic and mitral atresia; only 2 of 40 cases in which these data are provided survived beyond the first month. On the other hand, among the 11 cases of isolated mitral atresia in which data concerning the age of death is available, 4 survived the first month of life, although none lived longer than four months. The explanation for this longer survival time may lie in the increased amount of mixed arterial-venous blood which is permitted to pass into the aorta via a ventricular septal defect and dextroposition of the aorta. Perhaps this circulatory arrangement provides a better supply of partly oxygenated blood to the coronary arteries and forestalls the onset of cardiac failure by removing to some degree the ill effects of anoxia on the myocardium itself. In those instances of marked hypoplasia of the first portion of the aortic arch associated with aortic valvular atresia, retrograde flow of blood from the patent ductus arteriosus to the coronary vessels is minimal, and an early death may be anticipated. Thus the length of life in these infants may vary not only with the size of the interatrial communication, as has been pointed out by Roberts,[18] but also to some extent with the adequacy of the coronary blood supply. Several extracoronary sources of blood are available to the myocardium, but these probably play a limited role.

The apparently acyanotic, symptom-free state demonstrated by some of these infants during the first few days or weeks of life, together with the lack of roentgenographic evidence of cardiac enlargement, should lead one to offer a guarded prognosis in any newborn infant with congenital heart disease, whether or not cyanosis exists. The prediction of the presence of a relatively benign lesion on the basis of normal heart size and lack of cyanosis may be disconcerting when the sudden onset of congestive failure and cyanosis intervenes.

SUMMARY

The subject of congenital hypoplasia of the left heart with nonfunctioning left ventricle is reviewed. A classification of the various pathologic types of this malformation is suggested, based on the valvular deformities involved.

Two previously unreported cases of congenital hypoplasia of the left heart associated with mitral atresia and no aortic valve deformity are presented, with descriptions of

necropsy findings. In addition, four cases of combined aortic and mitral atresia or stenosis with hypoplasia of the left heart are presented.

The clinical histories, physical findings, and roentgenographic and electrocardiographic findings in these cases are reviewed and discussed.

While the diagnosis of hypoplasia of the left heart may be suggested by the roentgenographic findings during life, the differentiation of the various pathologic types from each other cannot be accomplished by clinical means available at the present time. The application of angiocardiography to this problem deserves further consideration.

Dr. James S. Forrester placed at our disposal the pathological material in Case 3, and Dr. Irving J. Wolman gave permission for the review of the cardiac specimens in the remaining cases.

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Case Reports

POLIOMYELITIS IN PREGNANCY, FETUS, AND NEWBORN

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IN THE FALL of 1954, a 20-year-old woman developed acute anterior poliomyelitis. She was at term, and the question of the fetus being affected before or at birth was raised. Also, nine days after diagnosis, when labor began, the question arose of whether she should be permitted upon the maternity service, and the neonate, in the nursery, of the local hospital. The mother had passed the seven-day isolation requirement of the state of California; it was felt that admission was reasonably safe.

A healthy boy was born. On the second day of life this infant developed poliomyelitis. Eleven other infants, concurrently in the nursery, were given gamma globulin. There were no observed secondary cases.

POLIOMYELITIS IN PREGNANCY

Susceptibility to and incidence of paralytic poliomyelitis appear increased in pregnancy.

In 95 cases collected by Aycock,* Fox and Sennett,[3] and Waaler,[4] wherein accurate comparison with the nongravid female population appeared possible, the reported incidence was 63% higher than among the nonpregnant female population of similar age.

An even greater increase in incidence was reported by Hunter and Millikan.[5] They found, from data of Baker and Baker,[6] Taylor and Simmons,[7] Shelokov and Weinstein,[8] and Priddle and co-workers,[9] that between 6.2% and 11% of women in the reproductive age will be pregnant at any one time. Yet in their series of 1148 patients admitted to the Mayo Clinic with acute anterior poliomyelitis, which included 190 women of reproductive age (15 to 45 years of age, inclusive), 34% of the affected married women and 26% of all the affected women of reproductive age were pregnant. Priddle and co-workers [9] found in the Detroit epidemics of 1949 and 1950 that 17.2% of females of reproductive age with poliomyelitis were pregnant. Bowers and Danforth,[10] in their series of 140 women with acute poliomyelitis between 15 and 47 years of age, found 24, or 17%, who were pregnant. They felt that authentic data upon the increased incidence of poliomyelitis were still lacking, as did Horn,[11] who challenged the validity of deductions such as these.

Nevertheless, other authors have alleged a true increase of incidence of poliomyelitis in pregnancy. This has remained unexplained, although Weinstein, Aycock, and Feemster [12] postulated a hormonal influence. Shaw † considers pregnancy one of the stress factors, along with fatigue, chilling, overexertion, operations, immunizations, and menstruation, which increase susceptibility to poliomyelitis.

There is no longer felt to be a predisposition according to trimester. The mortality rate in comparison to the nongravid female has varied, but is higher and highest in the third trimester and puerperium. In patients surviving the disease, the severity and extent

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Because of lack of space, some of the references have been omitted from the JOURNAL and will appear in the author's reprints.

Dr. Edwin H. Lennette, Dr. Rustin McIntosh, Dr. Edward B. Shaw, and Dr. Philip M. Stimson gave suggestions and criticism in preparation of this article.

Dr. Lennette, Chief of the Viral and Rickettsial Disease Laboratory, California State Department of Public Health, Berkeley, undertook the laboratory studies, the cost of which was defrayed from funds available under a grant from the National Foundation for Infantile Paralysis, Inc., to the California State Department of Public Health for support of research on the efficacy of poliomyelitis vaccines.

* References 1 and 2.

† Shaw, E. B.: Personal communication to the author, Feb. 24, 1955.

of paralysis and incidence of residual paralysis approximates that in the nongravid female.[10]

FETAL POLIOMYELITIS

At the same time that poliomyelitis in the gravid female occurs with an incidence greater than or equal to that found in the general adult population, fetal poliomyelitis is rare.

Harmon and Hoyne [13] failed to find poliomyelitis virus in a fetus dead as a result of maternal poliomyelitis and felt that death was due to anoxia rather than infection. They reviewed the literature on the effect of maternal poliomyelitis on the fetus and agreed with Kleinberg and Horwitz [14] that a normal course of pregnancy and labor and normal offspring may be anticipated.

The findings of Aycock and Ingalls [15] on the effect of maternal poliomyelitis upon the fetus show no fetal poliomyelitis. They do show, however, a hazard to the fetus in stillbirth and abortion, especially if the maternal poliomyelitis occurs in the second or third month of pregnancy. Bowers and Danforth [10] found a similar "pregnancy wastage" in one-third of their series of pregnancies, including five spontaneous abortions, two stillbirths, and one neonatal death, and a significant reduction of birthweight and retardation of development in those infants whose mothers had poliomyelitis in the first or second trimester.

Schaefer and Shaw [16] report a high incidence of abortion among their patients with poliomyelitis in early pregnancy. Anderson and co-workers [17] followed 75 patients with poliomyelitis, known to be pregnant. Eight died, and 16 of the surviving 67 aborted, an incidence of 24%. In Horn's [11] series of 180 patients who had poliomyelitis in pregnancy, the incidence of abortion was high only in those mothers who were critically ill or dying. Excluding these, there was an abortion rate of but 7%. Anderson and co-workers,[17] studying the 53 live infants born in their series, found but 2 with congenital anomalies, 1 with pyloric stenosis, the other with a paralysis of one eyelid, which lasted one month.

Bodian [18] and Horstmann [19] have demonstrated experimentally that viremia may occur, and Bodian presents evidence that it plays an important role in clinical infection. Schaeffer and co-workers [20] report the case of a 24-year-old woman who aborted 11 days after a clinical attack of poliomyelitis. Poliomyelitis virus was demonstrated in both fetus and placenta. They conclude that the virus reached the fetus and placenta during the stage of viremia. With the exception of the above, reports of pathologically demonstrable poliomyelitis in aborted embryos and fetuses and of sequelae of antenatally experienced disease in infants born of poliomyelitic mothers have not been found in the literature.

The findings of Miller and Wenner,[21] wherein 13 of 14 children with clinical poliomyelitis (in the 14th there may have been an error in diagnosis) developed high neutralizing antibody titers as early as two days after the first symptom, may explain this circumstance: the maternal antibody crossing the placental barrier would offer protection to the fetus from her infection.

POLIOMYELITIS IN THE NEWBORN

Falk,[22] in 1897, reported a 15-day-old infant with poliomyelitis. Since then, an increasing number of cases of neonatal poliomyelitis in infancy have been reported.‡ Abramson and co-workers [49] reviewed the literature and reported 4 additional cases, for a total of 30 cases under one month of age. Reviewing the non-Russian literature at this time, we have eliminated 2 cases [22] included in previous reviews, as the clinical data thereon are absent or incomplete, and found 30 additional cases. The additional case described in this report brings the total to 58. Principal features and documentation of these cases are summarized in Table 1.

Two infants were ill at birth; ours became ill at 40 hours of age, and five others became ill before the 5th day (the day of onset was unknown in four cases). The incubation period of poliomyelitis being generally held

‡ References 23-53.

TABLE 1.—*Review of the Literature on Poliomyelitis in Infants Under One Month of Age: Principle Features and Documentation*

Author	Year Reported	Time Onset Mother's Disease, Days Before or After Delivery	Time Onset Infant's Disease, Hr. or Days After Delivery	Contact, Other or None Known	Fever	Anorexia or Dysphagia	Listlessness	Diarrhea	Paralysis	C.S.F.	Sequelae
Falk [22]	1897	.....	15 days	None	0	..	+	0	+	None	Recovery
Peabody & co-workers [24]	1912	.....	2 wk.	?	..	..	..	..	0	.....	?
Gunewardene [20]	1918	.....	12 days	None	?	0	+	0	+	160 cells	Paralysis
Wernstedt [27]	1924	5 days after	5 days	(No details except died in 12 days)				..	..	.....	Death
	1924	.....	4 days	.....	..	..	+	..	+	.....	Recovery
De Fabritiis [25]	1930	.....	20 days	.....	..	..	..	..	+	.....	.....
	1930	.....	28 days	.....	..	..	..	..	+	.....	.....
Duchenne (from De Fabritiis) [25]	1930	.....	12 days	No data							
	1930	.....	4 wk.								
Fuks & co-workers [28]	1933	.....	2 wk.	None	+	+	+	0	+	None	Paralysis
Lance [29]	1933	.....	Birth	.....	..	..	Irritable	..	+	.....	.....
Cislaghi [30]	1934	.....	15 days	None	0	..	..	..	+	1+ Pandy "very occas. lymphocytes"	Paralysis
de Lange [21]	1935	Mother had fever 5 days after delivery	15 days	None	0	..	..	0	+	None	Death
Alsén [32]	1939	3 years before	20 days	.....	0	..	+	0	+	None	Paralysis
Severin [33]	1939	None	7 days	.....	..	..	..	0	+	Positive	Death
Gracoski & Hurmuzache [34]	1940	.....	21 days	None	+	..	Irritable	0	+	7 cells 4+ Pandy	Recovery
Biermann & Piszczek [35]	1944	1 day before (died)	11 days	.....	+	..	+	..	+	57 cells	Death
Palmstierna [36]	1945	M died at sect.	12 days	.....	..	..	..	..	+	Positive	Paralysis
	1945	7 days after	12 days	.....	..	..	..	..	..	Positive	Recovery
Frøvig [37]	1947	2 days after	5 days	Several	+	0	..	..	+	.....	.....
Buccellato [38]	1947	None	20 days	.....	0	0	0	0	+	300 lymphocytes	Death
Horn & Weidenthal [39]	1948	.....	3 wk.	Neighbor	+	+	+	..	+	? cells 3+ Pandy	Death
Johns [40]	1948	1 yr. before	5 days	Siblings	+	+	+	..	+ (Twitching)	.....	.....
Mouton & co-workers [41]	1950	9 days after	14 days	.....	+	0	0	..	+	37 cells	Paralysis
	1950	None	16 days	None	+	+	+	..	+	107 cells	Paralysis

TABLE 1.—*Review of the Literature on Poliomyelitis in Infants Under One Month of Age: Principle Features and Documentation*—Continued

Author	Year Reported	Time Onset Mother's Disease, Days Before or After Delivery	Time Onset Infant's Disease, Hr. or Days After Delivery	Contact, Other or None Known	Fever	Anorexia or Dysphagia	Listlessness	Diarrhea	Paralysis	C.S.F.	Sequelae
	1950	None	15 days	None	0	0	0	..	+	8 cells	Recovery
	1950	None	18 days	Sibling	0	+	+	..	+	85 cells	Paralysis
	1950	None	16 days	None	0	0	0	..	+	None	Paralysis
Baskin & co-workers [42]	1950	4 days before	3½ days	.....	+	+	+	..	+	106 cells	Death
	1950	2 days after	8 days	.....	+	+	+	..	+	.....	Death
	1950	.....	2½ wk.	Uncle	..	..	..	..	+	.....	.....
Kreibich & Wolf [43]	1950	16 days before	Bef. birth	.....	0	..	+	..	+	Autopsy	Died 12 hr.
Shelokov & Weinstein [8]	1951	3 wk. before	6 days	.....	+	+	+	+	+	Positive	.....
Aycock (from Shelokov [8])	1951	5 days before	1 day	.....	..	..	..	..	+	(Personal communication to Shelokov; no further data)	
Campos (from Shelokov [8])	1951	.....	3 days								
	1951	.....	5 days								
Johnson & Stimson [44]	1952	6 wk. before	4 days	Neighbors	..	..	..	..	+	16 cells	Recovery
Wright & Owen [45]	1952	1 day before	8 days	.....	..	+	+	..	+	356 cells	Death
McConnell [46]	1952	.....	16 days	None known	..	+	+	..	+	Autopsy	Death
Smallpeice & Ounsted [47]	1952	.....	2 wk.	Nursery Nurse	+	..	Irritable	..	+ (Convulsion)	140 cells	.....
	1952	.....	9 days	Nursery nurse	+	+	+	..	+	.....	.....
Phillips & Paschal [48]	1952	.....	13 days	.....	0	+	+	+	+	Autopsy	Death
Abramson & co-workers [49]	1953	2 days after	5 days	.....	0	..	+	..	+	30 cells	Death
	1953	Day of delivery	7-10 days	.....	+	+	+	..	+	78 cells	Death
	1953	2 days before	6 days	.....	+	0	0	..	+	53 cells	Recovery
	1953	None	10 days	None	+	+	+	..	+	None	Paralysis
Hagberg & Herlitz [50]	1953	1 day after	10 days	.....	..	0	+	..	+	56 cells/180 mg. protein	Recovery
	1953	.....	8 days	None	0	+	+	..	+	28 cells/240 mg. protein	Paralysis
Geffen & Tracey [51]	1953	M died 6 days postpartum	8 days	.....	..	..	..	..	..	.....	Death
	1953	.....	13 days	.....	..	No data on symptoms			..	.....	Death
	1953	.....	14 days	.....	..	..	..	..	..	.....	Death
	1953	5 days after	10 days	.....	..	..	..	..	..	.....	Paralysis
	1953	.....	"Newb. baby"	.....	..	..	..	..	..	.....	Death
	1953	.....	"Newb. baby"	.....	..	..	..	..	..	.....	Death
	1953	.....	"Newb. baby"	.....	..	..	..	..	..	.....	Recovered
Vonderweidt & Vergnet [52]	1953	.....	17 days	.....	..	..	..	..	..	.....	Death
Swarts & Kercher [53]	1954	1 day before; died & sect.	10 days	.....	..	+	+	..	+	500 cells	Death
Present report	1955	9 days before	1 day	None	+	0	0	0	+	280 cells	Recovery

to be 6 to 18 days, it is presumed that these represent cases of transplacental infection. Some of the others may, as well, though it is impossible in the light of present knowledge to assess this question completely. The majority of infants, however, acquired their infection at the time of or after birth, a conclusion based on the relative absence of infants ill at birth or in the first five days, regardless of presence or absence of maternal infection.

REPORT OF CASES

On Sept. 8, 1954, J. B., a 20-year-old woman, developed headache, nausea, vomiting, and fever. The fever lasted three days, and after its subsidence the patient developed weakness in the left lower and both upper extremities, reaching a maximum degree on Sept. 15.

She was pregnant, with her expected date of confinement Oct. 2. On Sept. 17 she went into labor, and, after consultation with the local health department,§ she was admitted on the obstetrical service of the Peninsula Community Hospital, Carmel, Calif., where at 3:22 p. m. a 7 lb. 9½ oz. boy was born. Examination at the time of birth revealed an active, alert, symmetrically well-developed infant without defect or abnormality. Neurological examination on Sept. 18 showed all muscle groups well formed, no abnormal spasticity or weakness. Ankle jerks and biceps jerks were equal and active. Knee jerks and triceps jerks were not elicited. It was not felt, however, that these findings represented illness, as muscle tone was good, but merely the often-encountered difficulty in eliciting deep reflexes in the newborn infant. The baby was first taken to the breast when 14 hours old.

On Sept. 19 (40 hours old) the baby developed fever, the temperature varying between 99.8 and 100.8 F. (Body temperature of other infants in the nursery was 98.6 F or below.) He was reexamined, with findings as before except that the knee jerks were symmetrically brisk. During the day, weakness appeared in the left calf and hamstring muscle groups.

On Sept. 20 all deep reflexes were absent. The baby was irritable, and the lower extremities were limp and flaccid, with active motion limited on the right and minimal on the left.

Attempts at spinal puncture on Sept. 20 and 21 were unsuccessful, a bloody tap being made. On Sept. 22 spinal puncture showed 280 WBC, 7% polymorphonuclears, and 93% lymphocytes. Red blood cells were present, and spinal fluid protein was not determined. Peripheral blood cell count showed RBC 5.59, Hgb. over 18.0 gm. per 100 cc., WBC 12,300, neutrophiles 12%, eosinophiles 16%, lymphocytes 72%.

The baby continued to nurse well. The flaccidity of the lower extremities decreased steadily. On Sept. 24 a muscle evaluation showed many areas of muscle weakness in both lower extremities and probable weakness in the right upper extremity, though it was felt that the upper extremities could not be adequately evaluated at this age. Both ankle jerks and the right knee jerk were elicited.

On Nov. 21, virological studies (Table 2) were undertaken on the blood and stools of mother and baby.‖ These studies showed neither mother nor baby possessing humoral neutralizing antibodies to Type I or Type II poliomyelitis virus. The titer of neutralizing antibody to Type III poliomyelitis virus, the third known immunologic type, was in both cases 1:256. Attempts at isolation of poliomyelitis virus from the stools of mother and infant were unsuccessful.

TABLE 2.—*Summary of Poliomyelitis Virological Studies on Mother and Baby*

Patient	Onset Illness	Blood Specimen for Test, Days After Onset	Neutralizing Antibody Titer to Type I Virus	Neutralizing Antibody Titer to Type II Virus	Neutralizing Antibody Titer to Type III Virus	Virus Isolation Attempts from Stool: Days After Onset	Virus Isolation Attempts from Stool: Results
Mrs. J. B.	9/ 8/54	79	<1:4	<1:4	1:256	74	Negative
Baby B.	9/19/54	62	<1:4	<1:4	1:256	64	Negative*

* Stool toxic for monkey-kidney-cell tissue cultures.

§ California State Law requires isolation for seven days from onset of illness, or for the duration of fever, if longer.

‖ Serum specimens were examined by the metabolic-inhibition method using trypsinized monkey-kidney cells as the tissue culture substrate. A toxic factor, which could not be destroyed or removed and which caused nonspecific cytopathic changes in the test tissue cultures, was found in the baby's stool. This, as well as the two-and-one-half-month interval between clinical illness and collection of material for study, may account for failure to isolate poliomyelitis virus from the infant's stool.

COMMENT

Poliomyelitis has been felt in the past to be unusually common in pregnancy, absent in the fetus, and rare in the newborn.

Poliomyelitis in Pregnancy.—Until and unless it can be demonstrated that the true incidence of all forms of poliomyelitis, including subclinical poliomyelitis, is increased in pregnancy, the most that can be said is that the observed and reported incidence and the number of hospital admissions, are increased. The close medical surveillance to which the gravid female is submitted, the greater concern which she and society feel for her care, and the probably concurrent better case reporting, may until that time explain the apparent increase. For the present, the question of the true incidence of poliomyelitis in pregnancy remains unanswered. If it is increased, Shaw's ¶ view, that pregnancy is a stress factor, appears the most satisfactory.

It was once thought that poliomyelitis was commoner in certain trimesters; it even appeared to Aycock [2] that the sex of the fetus might play a role. Larger series have shown neither to be true. There appears to be, however, a greater maternal mortality in the third trimester and puerperium,[10] a finding compatible with the physiological impositions of terminal pregnancy and the physical demands of labor and delivery.

Fetal Poliomyelitis.—The fetus can acquire poliomyelitis,[20] but it is more likely to be affected by illness in the mother in the second and third months, by mechanisms of a noninfectious nature, possibly anoxia # but more probably some effect on the fetus by the infection in the mother comparable to that found in other virus diseases.*

Why is the fetus so almost universally protected from infection? Two possible answers are available: one in the work of Miller and Wenner,[21] the other in the concepts of infection elucidated by Bodian.[18] Miller and Wenner showed that the mother acquires high neutralizing antibody titers as early as two days after onset of symptoms, and it is known that these are passively transferred to the infant.[54]

Bodian [18] showed that poliomyelitis is acquired through the alimentary tract and that the central nervous system infection is a chance, occasional, and apparently localized occurrence, the result of viremia. The fetus, free of a constantly present alimentary focus, may then not have the persistence or intensity of viremia present in the mother, but rather an occasional one, though the placental barrier, of such limitation and attenuation as to protect him from central nervous system invasion and clinical disease.

Neonatal Poliomyelitis.—Instances of congenital poliomyelitis are rare.† but they do occur. Whether those infants, well at birth but developing poliomyelitis before the sixth day of life, represent cases of congenital poliomyelitis cannot be stated. With the exception of the case of Wernstedt,[27] however, reported in 1924, in all cases wherein information on the mother was available she had a recent or concurrent poliomyelitis infection. The evidence in these cases would permit, therefore, if not favor, a transplacental congenital infection.

The majority of cases of neonatal poliomyelitis acquired after the sixth day probably represent extrauterine infection. That this can occur through birth-canal infection (alimentary tract to alimentary tract), or even at Caesarean section (maternal blood to infant's alimentary tract), has been shown by the reports of Biermann and Piszczek,[35] Palmstierna,[36] and Swarts and Kercher,[52] where the infant had no contact with his mother after Caesarean section or birth-canal delivery.

Why have there been so few reported cases of neonatal poliomyelitis? The question has long engaged the attention of investigators, and there appear to be several answers. First, immunity to the disease is widespread among

¶ Shaw, E. B.: Personal communciation to the author, Feb. 24, 1955.

Shaw, E. B.: Personal communication to the author, Feb. 24, 1955; Reference 14.

* Shaw, E. B.: Personal communication to the author, Feb. 24, 1955.

† References 29 and 43.

adult populations, and there is a passive transmission of immune bodies to the young through the placenta.[84] Secondly, the disease is difficult to diagnose, and the diagnosis is rarely made in the absence of widespread paralysis or death. Thirdly,‡ the course of the disease may be quite different from that in the older child or adult so that active infection may escape clinical recognition. Finally, the infant may not be protected so much by passive antibodies as by a relative insusceptibility of his tissues to infection at this age.

Excepting our own case, where the disease was anticipated, and the case of Hess, Levinson, and Hess,[85] that of a 4-month-old infant whose sibling had had poliomyelitis, we find no recorded instance of the diagnosis being made in the preparalytic stage in a patient less than 6 months of age.

SUMMARY

The incidence of poliomyelitis appears to be increased in pregnancy. This increase may be apparent, rather than real.

The mortality of poliomyelitis in pregnancy is increased at term and in the puerperium; otherwise the severity of the disease, the mortality, and the frequency of residual paralysis approximate those of the nongravid female.

Fetal wastage due apparently to noninfectious factors occurs, especially in the first two trimesters, but its reported incidence has varied and appears related to severity of maternal illness.

Fetal poliomyelitis is rare. Possible explanations for this are presented.

Poliomyelitis in the newborn is not rare, but passive transfer of maternal antibodies and difficulties in diagnosis in the newborn have made the diagnosis uncommon. Fifty-seven cases occurring in the first month are collected, and a case occurring in a 40-hour-old infant is presented, appearing to be the earliest reported case in an infant well at birth.

920 Cass St.

‡ Shaw, E. B.: Personal communication to the author, Feb. 24, 1955.

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BENIGN TERATOMA OF THE STOMACH IN AN INFANT

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TERATOMAS arising from the stomach have been the subject of two published reports. Selman,[1] in 1943, reported the case of an infant who was submitted to surgery at the age of 4 months because of an abdominal mass occupying the upper left quadrant. At operation, a fibrocystic mass 6 in. in diameter was disclosed, arising on a broad base from the anterior wall of the stomach. Removal of the mass and the portion of stomach wall from which it arose effected a cure. The tumor contained a variety of tissues, including skin and appendages, connective tissue, and colonic mucosa. It was a benign, complex teratoma. Selman's survey of the literature failed to disclose any previous case described by those interested in teratomas or benign gastric tumors.

Large, Williams, and Neel encountered a similar tumor in a 7-month-old infant, in 1952.[2] This child's hemoglobin was 4 gm. per 100 cc. following hematemesis and passage of tarry stools. At operation a 5 cm. tumor was found to involve the posterior wall of the antrum and to project largely into the stomach. The mass was presumed to be a duplication of the stomach, and a partial gastrectomy was carried out. Microscopic examination of the tumor revealed ectodermal, endodermal, and mesodermal elements, and it was felt that the tumor was a typical benign teratoma which had caused the overlying gastric mucosa to be ulcerated.

This report concerns a third case of teratoma arising from the stomach. The case is similar to those previously reported in that the patient was a baby boy, the tumor benign, and the cure surgical. However, an early misdiagnosis obscured the proper course of therapy when the lesion was first seen.

Submitted for publication May 6, 1955.

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REPORT OF A CASE

J. W. (J. H. H. 695033), a 4½-month-old boy, was admitted to The Johns Hopkins Hospital on Jan. 23, 1955, because of an abdominal tumor.

The family history was unremarkable, and the past history revealed that a hernia repair had been performed in the left inguinal region when the child was 9 weeks old.

Two weeks prior to his admission the child was referred to a pediatrician because of increasing abdominal girth for one week. Constipation, anorexia, and fever were also noted concurrently. At this time the child seemed weak and poorly developed and had a protuberant abdomen. A mass which was visible across the whole upper abdomen extended to within 2 cm. of the umbilicus. Because it had a firm rounded edge and because of the way it moved during respiration, it was thought to be the liver. Two examiners thought it could be distinguished from the liver.

X-ray confirmed the presence of the mass and revealed many areas of calcification (Fig. 1). Intravenous pyelography showed downward displacement of the left kidney.

Four days later, on the presumptive diagnosis of neuroblastoma, a needle aspiration was carried out. This was thought to confirm the diagnosis. The patient continued to run fever and lose weight. Five days prior to admission to the hospital, x-radiation therapy was begun and administered over three days, without effect. Because of the strong desire on the part of the pediatrician that the child be offered the benefits of surgery, the child was transferred after receiving generous blood transfusions.

Physical examination at the time the patient was admitted revealed essentially the findings outlined above.

The hemoglobin and white blood cell counts were normal, as was the urinalysis.

X-ray study of the skull and long bones was made to supplement the previous x-ray studies. No evidence of metastasis was found.

Operation (J. C. H.).—Exploratory laparotomy was carried out on Jan. 28, 1955, with the patient under vinyl ether (Vinethene)-ether-oxygen anes-

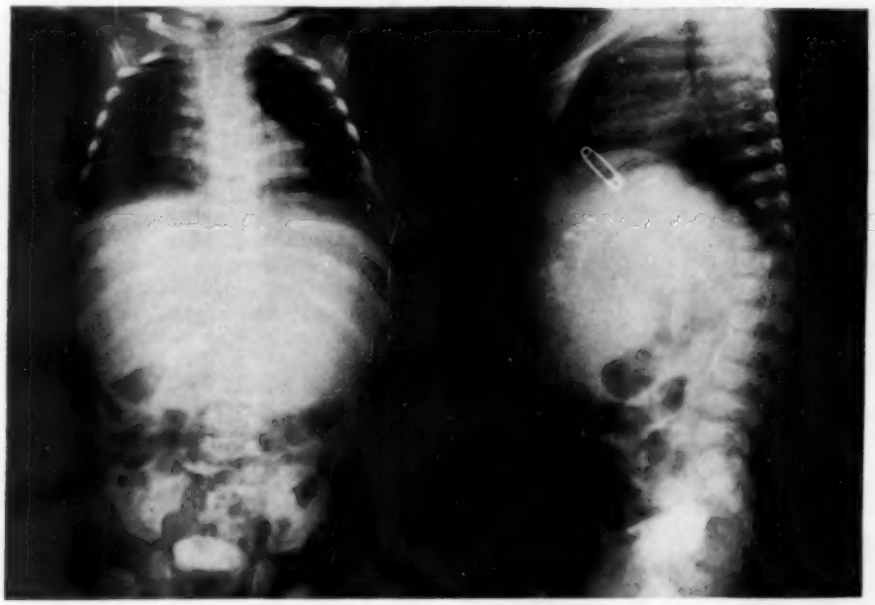

Fig. 1.—In the anteroposterior and lateral projections a large mass is seen to occupy the upper anterior abdomen. There are prominent, extensive areas of calcification visible within the mass.

Fig. 2.—The specimen, as viewed from its posterior aspect, demonstrating the disk of gastric mucosa with which it was removed. The tumor itself is covered by a glistening serosa. Lobulation and variations in color and texture are evident.

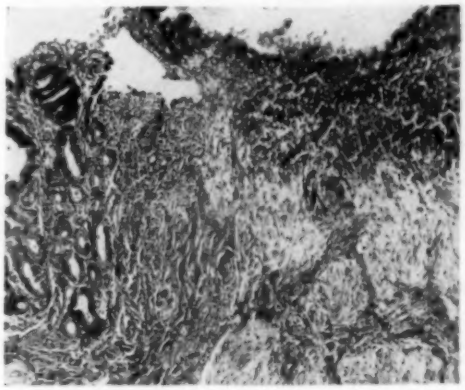

Fig. 3.—Normal gastric mucosa is seen to merge with an ulcer filled with granulations in this section through the gastric mucosa. Brain tissue is visible in the submucosa; reduced approximately ½ from mag. × 100.

thesia. The abdomen was entered through a long upper abdominal transverse incision. A massive lobulated gray-white tumor immediately presented into the wound and filled it. This tumor had gross cystic areas, extensive calcification, and firm and fibrous tissues. The liver and spleen were uninvolved, the mass occupying the whole of the area between liver and transverse colon. It was delivered and could be demonstrated to arise from an area 7.5 cm. in diameter on the anterior wall of the stomach. Light attachments between the gastrohepatic ligament and the gastrosplenic ligament and the mass were divided, and the disc of wall of the stomach from which the tumor arose was excised with the mass. The stomach was closed transversely.

The postoperative course was uneventful, the child being discharged on the ninth postoperative day.

Pathology Report.—The mass was an irregular, lobular tumor which weighed 250 gm. and measured

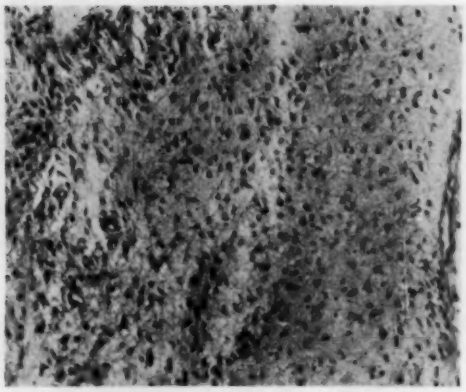

Fig. 4.—A section through one of the numerous areas of brain tissue in the tumor. Aspiration biopsy from one of these areas led to an erroneous diagnosis of neuroblastoma; reduced approximately ½ from mag. × 200.

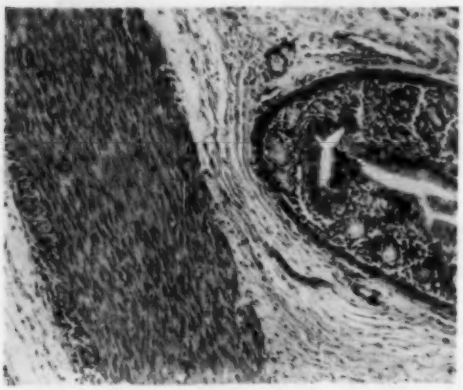

Fig. 5.—Colon mucosa is underlain by a bar of muscle; reduced approximately ½ from mag. × 150.

Fig. 6.—A section of tooth and a section of bone are separated by loose areolar tissue; reduced approximately ½ from mag. × 50.

12×8×6 cm. The surface was smooth and shiny except for an area 4 cm. in diameter, which appeared to be mucosa and which was intimately attached to the mass. The cut surface presented a varied appearance; there were cystic spaces containing clear or mucoid fluid; areas of brown, soft tissue, and fibrous gray-white tissue (Fig. 2).

Microscopic Notes.—The patient's gastric mucosa was seen to merge with an ulcerated area lined with granulation tissue (Fig. 3). Underlying this area there was nervous tissue resembling brain where muscularia would ordinarily lie (Fig. 4). Other sections reveal intestinal mucosa, respiratory mucosa, muscle, bone, and teeth (Figs. 5 and 6).

COMMENT

In this case, the third one of teratoma of gastric origin to be presented in the literature, a serious error in treatment was narrowly averted. A needle biopsy of the tumor had apparently yielded brain as a specimen, and microscopic examination of this tissue lent credence to the presumptive diagnosis of neuroblastoma. To have pursued a course of x-ray therapy further would have been especially ironic when one considers the ease with which this child was cured by surgical measures.

The three cases have certain features in common which may be worthy of repetition. All were in baby boys under one year of age. In two instances, anemia has been an outstanding symptom, presumably due to superficial ulceration of the gastric mucosa. In two instances the increase in abdominal size first attracted attention. The three tumors were all "tridermal," containing elements felt to be derived from all three germ layers, and all three were benign. Finally, all were readily amenable to surgical ablation.

SUMMARY

A case of benign tridermal teratoma of gastric origin is presented. Two previous case reports have appeared in the literature. Common features of the cases are discussed.

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STRYCHNINE POISONING

Case Report of Fatality in a Fifteen-Month-Old Child

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THE ROLE of strychnine in homicide and suicide is well established in the annals of legal medicine and toxicology. Occasionally strychnine is featured as the agent in accidental poisonings, the most tragic being those cases involving fatalities in children due to their ingestion of some candy-coated proprietary drug or medicine containing the poison. This communication is an account of such a case.

REPORT OF CASE

A 15-month-old white boy had been playing in his parents' bedroom. The parents noticed that the infant looked ill, and he cried out as if in pain. These symptoms were followed by jerking movements and appearance of a blue coloration of the skin. The baby was rushed to the nearest medical facility, and while en route it was necessary for the father to administer artificial respiration on two separate occasions.

As the child had been seen playing with "camphor balls," a history of suspected poisoning was given. Gastric lavage was accomplished, and oxygen was administered, followed by caffeine and sodium benzoate.

Physical examination revealed a child in an acute convulsive state, with respiration short and rapid; there were generalized arm and leg muscular twitchings. Apex heart beat was rapid, weak, and irregular. No wrist pulse was felt. Severe cyanosis existed. The pupils were markedly dilated and showed no response to light and stimulation. A tepid enema was given. One gram of phenobarbital sodium was administered as convulsions and cyanosis persisted. Although the baby's color appeared somewhat better, the extremities remained cyanotic. A few minutes later a general cyanosis set in. More oxygen and caffeine and sodium benzoate were given.

The child began to vomit a brown liquid substance, relaxed generally, and died, despite artificial respiration and stimulation of heart with epinephrine. Time of death was 30 minutes after being brought into dispensary. Diagnosis was recorded as acute respiratory failure caused by a continuous convulsion of approximately 45 minutes' duration.

History given by the parents was noncontributory, indicating a normal birth and perfect health since birth. The child had eaten a normal breakfast four hours before being stricken.

Pathology reports, including gross and microscopic studies, were all normal and could contribute nothing to establish a definite cause of death. Complete liver and all available gastrointestinal contents were saved for toxicological analysis. Stomach washings were inadvertently discarded in the confusion of emergency treatment.

Investigation by police and parents revealed that 9 out of an estimated 40-50 chocolate-coated laxative tablets remained in a pillbox in the night table near the mother's bed, the area in which the child had been playing prior to the onset of first symptoms. The parents were certain that the child had consumed the missing tablets, which were frequently used as a mild laxative. The pillbox and the remaining pills were submitted, with autopsy tissue mentioned, for toxicological analysis.

Laboratory Investigation.—The label on the pillbox bore the inscription "PHENALOIN, 1 or 2 as needed." From the nature of the pills and the stem words in the name, the presence of phenolphthalein and aloin were presumed. Chemical tests revealed the presence of phenolphthalein in the chocolate-coated pills and in the chocolate-colored gastrointestinal contents.

Through pharmaceutical trade journals the manufacturer was located and requested to furnish the formula and prescription of the laxative pills in question. Reply from the firm indicated each tablet to contain six ingredients, among which were phenolphthalein, aloin, belladonna (total belladonna alkaloids approximately 0.1 mg.), and strychnine sulfate, the latter in the amount of 1/60 grain (approximately 1 mg.) for each brown-coated tablet.

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From the Toxicology Section, USAREUR Medical Laboratory, Landstuhl Army Medical Center, Landstuhl, Germany. Present address: Valley Forge Army Hospital, Phoenixville, Pa. (Capt. Leifheit); Glens Falls Hospital (Dr. Knopp).

At the time these determinations were made, the technique of paper chromatography and ultraviolet absorption were not as yet routinely employed. Therefore, classical color reactions were used.

Color tests, using sulfuric acid and potassium dichromate, and crystal tests, employing picric acid, gold chloride, and Marme's cadmium-iodide and potassium iodide reagent, indicated the presence of strychnine in the alkaline ether extract of both the pills and the gastrointestinal contents.[1] A similar extract of the liver failed to yield definite positive results for strychnine with such tests. However, this failure is attributed to the fact that death occurred about 50 minutes after the onset of first symptoms. This time interval was not sufficient to permit a build-up of strychnine in the liver in a concentration which would give positive results with the test mentioned.

The "frog test" yielded interesting results. Four frogs of equal weight and age were injected with neutralized extracts, dissolved in 0.9% NaCl solution, by the standard technique of injecting 0.5 ml. into the frog's dorsal lymph sac.[1] The Table lists the observations.

Results of Frog Tests

Specimen	Material Injected	Time Required for Appearance of 1st Strychnine Convulsion, Min.
A	Positive control—0.2 mg. pure strychnine sulfate	7.5
B	Pill—extract of part of one pill equal to approximately 0.3 mg. strychnine sulfate	5
C	Alkaline extract of approximately 440 gm. liver	10
D	Alkaline extract of approximately 10 ml. gastrointestinal contents	1.5

In the cases of A, B, and C, the frogs were killed by means of chloroform after the third convulsion. In the case of D, death occurred during the first and only strychnine convulsion. All frogs exhibited the classical strychnine reaction, i. e., nervousness and accelerated respiration preceding the first convulsion, followed by other severe convulsions, each readily set off by a stimulus of noise or jarring. Tests for atropine in the liver and gastrointestinal contents ranged from "negative" to "doubtful," which can be understood to be due to the presence of minute amounts of belladonna in the pills.

It must be concluded that, despite gastric lavage, the concentration of the strychnine sulfate in the small quantity of gastrointestinal contents far exceeded that of either the pill, the liver, or the positive control. Also, the quantity of strychnine absorbed must have been small.

COMMENT

The matter of fatal dosage for strychnine seems to be debatable, particularly in the older literature. The smallest fatal dose of strychnine has been reported to be 16 mg., having been fatal to a woman of 36 years in one and three-quarters hours.[2] The average fatal dose seems to be placed in the range of 90 to 120 mg., and the minimum fatal dose at 30 mg.* Unfortunately there seem to be no statistics on the average fatal absorbed dose.

This child was reported to have ingested from 30 to 40 chocolate-coated laxative tablets, each containing 1/60 grain of strychnine sulfate. This is equal to 0.5-0.7 grain (33-46 mg.) of the compound. As strychnine sulfate contains about 78% pure strychnine, these values recalculate to the ingestion of about 0.4-0.5 grain (26-33 mg.) of pure strychnine. On the basis of these facts, it is more than reasonable to assume that the ingested dose of strychnine was a quantity sufficient to be fatal to a 15-month-old child. As to laxative mixtures containing strychnine, the preparation mentioned in this communication corresponds closely to pills of aloin, strychnine, and belladonna, N. F. (A. S. B. pills). Strychnine supposedly stimulates peristalsis, but it possesses no appreciable action on intestinal musculature in therapeutic doses. Alkaloids in such mixtures act but a short period of time, and their effect passes long before the cathartic agents act. Unfortunately, such pills are marketed with a sweet coating and have, as we have seen, caused strychnine poisoning in children.[6]

SUMMARY

A case has been reported wherein a 15-month-old child ingested a sufficient number of proprietary chocolate-coated strychnine-containing laxative pills to die from strychnine poisoning.

*References 2-5; personal communication to the authors from the Toxicology Laboratories, Office of the Chief Medical Examiner, New York, 1950.

Simple laboratory investigations were conducted by which strychnine was isolated and established, along with clinical symptoms, as the cause of death.

Fatal dosages of strychnine are briefly reviewed and are compared with findings in this specific case.

The irrational use of strychnine in proprietary laxative pills, with inherent dangers, is discussed.

In spite of the presence of other compounds in the pills ingested by the child, the most active secondary to strychnine being belladonna, the typical symptoms of the victim, the short time before onset of symptoms, and the typical positive laboratory tests strongly indicate a typical strychnine death.

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CUTANEOUS CUTEREBRA MYIASIS

An Unusual Case in An Infant

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NEARLY every physician has at one time or another witnessed the contamination of a necrotic lesion by maggots, and in the early part of this century certain species of fly larvae were even employed therapeutically as scavengers. Myiasis is well known in domestic animals as a source of ruined hides, blown meat, and frequently fatal extensions of wounds. Specific parasitism by fly larvae in humans however, is not familiar to many physicians and is relatively uncommon in the United States. Infestation by the strictly American genus Cuterebra has been reported only twice, both instances involving adults. The present case in an infant, therefore, is unique.

Since failure to recognize this entity may lead to unwarranted concern, needless morbidity, and perhaps unnecessary or inappropriate therapy, it seems worth while to report the following episode in medical literature.

REPORT OF CASE

A boy, aged 11 months, in otherwise excellent physical health and hygiene, was noted to have a small macule in the anterior cervical triangle shortly after an automobile trip from Ann Arbor, Mich., to Seattle. The macule enlarged over a period of one month to a papule some 2 mm. in diameter, slightly inflamed and indurated, but lacking the usual signs of acute inflammation, including fluctuance, definite tenderness, or regional adenopathy. Minute serous discharge did occur without reduction in size, and upon close examination, a small umbilicate opening was discovered. The lesion continued to enlarge slowly, and a whitish base could be seen through the aperture, which appeared to move up and down

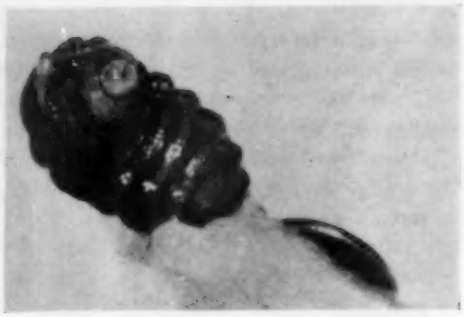
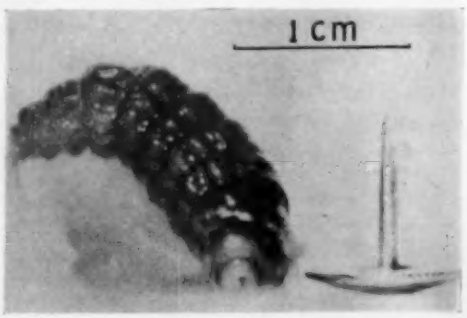


Fig. 1.—Caudal and ventral view of larva partially contracted and flexed. Note segmental stippled appearance. Color, dark brown.

in the opening depending upon intrapharyngeal pressure or external compression. There were no apparent symptoms, such as pain or itching. When the discharge became serosanguineous a surgeon was consulted. During his examination, the central core was expressed some 5 mm. through the thinned and taut aperture, appearing exactly like the posterior end of the larva shown in Figure 1. Although apparently obvious in retrospect, the correct diagnosis was not suspected. Necrotic abscess core, congenital or acquired fistula or sinus tract, and, remotely, neoplasm and foreign body were considered. Surgical excision was scheduled, and benzoin

Fig. 2.—Larva extended, cephalic end visible at top of photograph. Note mouth hooks momentarily withdrawn from piece of tissue.



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From the University of Washington School of Medicine; Instructor, Department of Radiology.

tincture was applied. The following morning the entire lesion appeared flatter and dry. A search of the bedding disclosed an actively moving larva, dark brown and finely stippled (Figs. 1 and 2). It apparently left the host because of the benzoin application. The wound healed uneventfully without further treatment.

Prof. M. H. Hatch, Department of Zoology, University of Washington, identified the living organism as a fly larva and recommended sending the fixed and preserved specimen to Prof. Maurice T. James, Department of Zoology, State College of Washington. Unwisely, an attempt to rear the larva was made which failed. The specimen was then sent to Professor James, who identified it as a larva of the genus Cuterebra, further determination not being possible.*

Parasitism in man by fly larvae is largely nonspecific, the larvae acting as scavengers or simply as contaminants in wounds and bodily orifices or tracts, although at times they may actually attack living tissue and produce serious disease. In distinction however, certain flies are obligatory parasites, that is, require living animal tissue to complete their life cycles. Many of these have been reported as producing myiasis in man, including the warbles, bot flies, certain flesh flies, and blow flies. Members of the genus Cuterebra normally parasitize rabbits and rodents, but occasionally attack cats and dogs. The two previously reported human cases involved the skin of the thorax [2] and the nares.[1]

The route of entry in specific cutaneous myiasis is variable. Eggs are usually deposited in the habitat of the host, but may be laid directly on or in the host. The hatched larvae may enter breaks in the skin or bodily orifices such as the eyes or nares, and some can actually penetrate the intact skin. Many flies can deposit already hatched larvae directly. An interesting situation obtains in a species closely related to Cuterebra (Dermatobia hominis) in which the female fly captures an arthropod carrier and deposits her eggs on its abdomen, where they eventually hatch. When the carrier, frequently a mosquito, bites a host, the larvae drop off and enter the wound.

Once in the skin, the larvae attaches itself by means of mouth hooks, and eventually the posterior end, bearing the respiratory spiracles, is forced out into contact with the air. It then passes through three stages of development, or instars, and finally leaves the host, drops to the ground, becomes a pupa, and completes its metamorphosis to an adult fly.

Cutaneous myiasis may be single or multiple, producing furuncular lesions with variable degrees of symptoms, or the larvae may burrow about under the skin, causing a creeping eruption.

Treatment consists of removal. In certain locations, such as the eye or mastoid cells, it may be complicated, particularly if the larvae are small, multiple, or active. Killing of the organisms in situ is frequently advised, but the means may lead to increased activity and pain or tissue damage and slough. Harrell and Moseley describe a unique method using infiltration with local anesthetic to inactivate the larva and produce regional anesthesia simultaneously.[4]

Identification is important, since complete information is lacking for many species and genera, and there is some correlation between severity and type of organism. Deaths have been reported. While rearing of the larvae to adult flies is helpful, it is usually not possible with obligatory parasites unless they have pupated. If only one specimen is recovered, it is probably better to obtain photographs recording as much detail as possible, fix the larva by immersion in boiling water, and preserve it in 80% alcohol for subsequent identification. If more than one specimen is available, some should be placed in a jar of moist sand or sawdust for rearing, care being taken to prevent contamination or subsequent escape of the fly.

Diagnosis, when the protruding end of the larvae can be seen, should be obvious, but, unless the possibility is considered, correct

* Professor James gave advice and help in preparing this report and the references to the literature, including his monograph on the subject of myiasis in man.[6]

interpretation may be overlooked. It is hoped that this report will stimulate or resuscitate the reader's interest in myiasis.

SUMMARY

Attention is drawn to the fact that many physicians are apparently unfamiliar with specific parasitism in man by fly larvae. An unusual case, in an infant, by the genus Cuterebra is reported. A brief discussion of the entity is included.

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PSEUDOHYPOPARATHYROIDISM

Report of Case in a Sixteen-Month-Old Girl

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and
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INTRODUCTION

IN THE year 1942, Albright, Burnett, Smith, and Parson [1] first reported three cases of pseudohypoparathyroidism which they termed Seabright Bantam syndrome because of the end-organ apparently being refractory to endocrine stimulation. This is a relatively rare condition. There are about 16 cases reported in the literature.* This report is Case 17 and is the youngest on record.

The syndrome is characterized by (1) hypocalcemia, (2) hyperphosphatemia, (3) manifestations of tetany, and (4) calcium deposits in the basal ganglia and subcutaneous tissue.[14] In this condition, biopsy shows normal parathyroid tissue and the patients fail to respond to parathyroid extract.

Clinically, the patient demonstrates a moon-shaped face, strabismus, short neck, brachydactylia due to early fusion of the metacarpals, obesity, and short stature. Respiratory symptoms, tetany, or other central nervous system manifestations may be present. Mental retardation is a common problem. The differential diagnosis must include Mongolism and cretinism.

Submitted for publication June 7, 1955.

From Children's Memorial Hospital, Omaha.

Associate in Pediatrics (Dr. Oberst) and Associate Professor in Pediatrics (Dr. Tompkins), University of Nebraska College of Medicine.

* References 2-13.

REPORT OF CASE

PATIENT W. I. F.—A 16-month-old girl.

Previous Infection.—Five days prior to admission, the patient had a generalized clonic convulsive seizure associated with an upper respiratory infection and a temperature of 100.4 F. There had been no previous episodes of seizures. The patient was slow to develop and was admitted for diagnostic studies.

Past History.—Hospitalized for diarrhea at 3 weeks of age for one month. Frequent upper-respiratory infections. Development: birth weight 6 lb. 5 oz.; sat at 6 months of age. Does not yet walk or talk. Has no teeth, can turn over, sits if passively set upright but does not rise to a sitting position on her own initiative. Does not stand, even

Fig. 1.—Poor concentration of iodopyracet (Diorast) after intramuscular injection. Rather slow uptake from thigh muscles and subcutaneous tissue leakage also. Both would indicate poor renal function and slow absorption.

with support. Takes 1 pt. of milk and a can of fruit per day. Does not accept any other solids.

Physical Examination.—Obese but underdeveloped white girl who appears to be about 8 months of age. Responds to any stimulus by crying irritably. Constantly sucks her (large) tongue when awake and drooling. Sleeps most of the time. Shows no interest in toys or other objects placed by her. Weight 22 lb., skin of good color and fine texture. Hair is thin and fine. The eyes reveal epicanthal folds bilaterally; pupils react equally and respond to light, intact, ophthalmoscopic examination normal. Ears, nose, mouth clear. No teeth have erupted. There is slight injection of the throat, tonsils Grade II-III hypertrophy. The neck is short but has no extra lateral skin folds. The chest reveals a normal heart and lungs. Examination of the abdomen reveals a liver 2 fingerbreadths below the right costal margin. Extremities show a flaccid tone, no spasm or atrophy apparent, reflexes physiological.

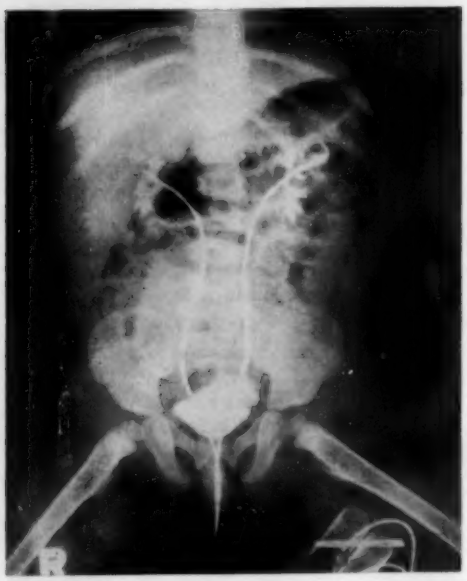

Fig. 2.—Retrograde pyelogram showing normal renal structures.

LABORATORY REPORTS

Hematology.—

Aug. 10: RBC, 5,110,000; Hgb., 12 gm. per 100 cc.; WBC, 12,400; segmented cells, 35; staff cells, 3; lymphocytes, 62

Sept. 14: RBC, 4,080,000; Hgb., 12 gm. per 100 cc.; WBC, 10,000; segmented cells 30; staff cells, 1; lymphocytes, 67; eosinophiles, 1; monocytes, 1

Blood Chemistry.—Oral glucose tolerance test: fasting 72.7; ½ hr. 111.1; 1 hr. 86.9; 2 hr. 85.1; 3 hr. 102.6

CO_2-combining power: 53.9 vol. %

N. P. N.: 45.7 mg. per 100 cc.

Total serum protein, 7.28; albumin/globulin, 5.31/1.97; ratio, 2.7:1

Alkaline phosphatase: 9.6 Bodansky units

Serum potassium: 5.31 mEq. per liter and 5.3 mEq. per liter

Blood calcium: 5.61 mg. per 100 cc.; 5.67 mg. per 100 cc.

Blood cholesterol: 146.5 mg. per 100 cc.

Spinal Fluid.—Colorless, clear, no elevation of pressure; 4 lymphocytes; sugar, 49.7 mg. per 100 cc.; protein, 25 mg. per 100 cc.; calcium, not determined

Tuberculin Patch Test.—Negative.

Serology.—Eagle test, negative.

Urine.—Clear straw color; specific gravity, 1.015; neg. for albumin, sugar, acetone, and sediment. Repeated five times, same results.

Concentration test unsatisfactory owing to technical difficulties.

Ellsworth-Howard test † positive for pseudohypoparathyroidism, showing a flat curve for excretion of urinary inorganic phosphate.[15] The results of the Ellsworth-Howard Test are shown in Table 1.

X-Ray Report (Aug. 10, 1953) ‡.—Films of the Bony Skeleton, Impression: Findings are consistent

† Parathyroid injection (Paroidin—Parke, Davis & Company) was used to perform the Ellsworth-Howard Test.

‡ X-ray interpretation and films supplied by Dr. Ralph C. Moore, Radiologist, Children's Memorial Hospital, Nebraska Methodist Hospital, and Associate Professor of Radiology, University of Nebraska College of Medicine.

TABLE 1.—*Results of the Ellsworth-Howard Test*

	Urine Phosphorus			
	Vol., Cc.		Mg./100 Cc. PO_4	
Specimen	Control	Patient	Control	Patient
1	75	25	0.16	0.32
2	375	60	0.02	0.01
3	360	80	0.03	0.03
4	300	150	0.13	0.02
5	275	130	0.16	0.02

	Serum Phosphorus, Mg./100 Cc.	
	Control	Patient
Fasting Serum, Hr.	7.2	8.0
2	5.6	7.0
4	4.9	7.0
6	4.7	8.1

with a generalized metabolic disturbance with demineralization of the bones but no arrest of bone growth. There are questionable atypical epiphyseal centers in the proximal ends of the proximal row of phalanges in the hands and there is frontal hyperostosis. There is no evidence of rickets or scurvy.

Intravenous Pyelograms and Retrograde Pyelograms.—Normal kidney function.

EEG Report (Aug. 12, 1953).—Resting Record: High voltage 2-4 cps waves are continuous in all tracings. No focal signs. No seizure discharges.

Sleep Record: There is no detectable difference between the waking and sleep records. No "sleep spindle" bursts occur.

Classification: Abnormal diffuse slow.

Treatment.—Treatment consisted of calcium and vitamin D in large dosages. Phosphorus determination and urinary Sulkowitch tests were done twice a week.

Clinical Course.—The patient showed gradual improvement with normal blood calcium and phosphorus levels after three weeks. Normal levels then were maintained through the remainder of the hospital course.

After only three days of treatment, the patient seemed mentally brighter and more alert. This improvement was obvious after the first week. The tongue protruded less, and there was no more drooling. The patient was awake longer and was happy, cheerful, and excessively friendly. Her appetite was good, and she took solids well.

Fig. 3.—Coarse trabeculation of bones of hands and wrists, with some shortening of the bone length. No rachitic deformity.

TABLE 2.—*Blood Calcium and Phosphorus Levels*

	Blood Calcium, Mg./100 Cc.	Blood Phosphorus, Mg./100 Cc.
8/11	5.67	...
8/13	5.67	...
8/25	8.4	7.6
8/26	7.0	8.0
8/27	7.0	...
8/29	7.5	7.7
9/ 1	7.9	6.9
9/ 5	7.6	6.2
9/ 9	9.3	3.6
9/11	10.8	4.9
9/15	10.4	5.2
9/19	10.3	5.2
9/23	10.7	4.5
9/28	9.8	3.5

X-Rays (Sept. 22, 1953).—X-rays indicated improvement.

Films of the Skull: The ossification of the skull appears more normal, with trabeculation in the frontal region and less prominence of the suture lines. The bones of the hands still appear quite osteoporotic, with widened medullary spaces and thinned cortices, but the epiphyseal ends of the radii and ulni appear more normal, with less flattening and irregularity of the metaphyses.

Impression: Findings would indicate improvement in the ossification of the bones since the previous examination.

At the time of discharge, the patient sat up alone, played actively with toys, waved goodby, and

Fig. 4.—Demineralization of the distal femoral ends especially in the metaphyses. Some demineralization of the fibulae and tibiae. Note also bands of transverse density across shafts of bones due to periods of temporary arrest of bone growth.

walked with support. The patient did not yet talk and still was edentulous. She weighed 20 lb. Dosage of vitamin D was decreased twice in the face of heavy turbidity of the Sulkowitch test. A moderate turbidity was considered ideal.

Follow-up Studies.—Follow-up studies at intervals reveal continued improvement physically and mentally. This covers a period of about 12 months (Table 3). Hgb, 13 gm. per 100 cc.; RBC, 4,390,000;

Fig. 5.—Generalized thickened frontal bone with "ground glass" appearance of calvarium.

TABLE 3.—*Follow-up Studies*

Date	Calcium, Mg./ 100 Cc.	Phosphorus, Mg./ 100 Cc.	Sulkowitch Test
10/ 8/53	9.5	3.7	Moderate turbidity
10/27/53	11.3	7.0	Negative
11/23/53	9.6	6.4	Negative
12/28/53	8.4	5.0	Moderate turbidity
1/28/54	11.3	3.9	Moderate turbidity
3/22/54	11.6	7.9	Moderate turbidity
7/19/54	12.0	2.2	Moderate turbidity

WBC, 7,000; sed. rate, 17 mm/hr. (Landau Method); age, 26 months; height, 30 in.; weight, 20 lb. 15 oz. Doesn't walk alone.

Fig. 6.—Same appearance of skull from postero-anterior view.

Present Treatment.—

1. Basic aluminum carbonate (Basaljel)—2 teaspoonfuls (8-10 ml.) q. i. d.
2. Calciferol—200,000 units q. 2 days.
3. Calcium powder—0.75 gm. t. i. d.

X-Ray Report (March 22, 1954).—Films of the Skull and Long Bones: The frontal bone still appears somewhat thickened but not as dense as at the time of the previous examination, and the trabeculations of the frontal bone are less prominent.

The long bones of the upper arms, shoulder girdles, thorax, lumbar spine and pelvis, and upper femurs are all normal in appearance. The tibiae and fibulae are normal in appearance, with none of

the evidence of generalized bony demineralization as noted at the previous examination.

Impression: The findings indicate considerable improvement, with the bony architecture at present nearly normal in appearance with normal development and ossification.

COMMENT

Prognosis in this condition is good from a life-span standpoint. The tetany and laryngeal stridor usually disappear, and the mental status tends to improve with treatment.

There seems to be a family trait involved in this problem, according to the cases reported in the literature. The bones may show both demineralization and a thickened cortex. This patient demonstrated both findings. Subcutaneous calcifications have been reported in 11 out of 14 cases.

The problem of the demineralization and thickened cortices is a complicated question.§

One function of the parathyroid hormone is to depress the renal threshold for the excretion of phosphate.[2] Accordingly, if a deficiency of parathyroid hormone exists or if the renal tubules fail to respond to the hormone as in pseudohypoparathyroidism, there will result a decrease in phosphorus excretion in the urine; secondarily, the serum phosphorus level rises. Almost simultaneously, the serum calcium level falls. With the fall in serum calcium, there is a diminished calcium excretion in the urine. The fall in serum calcium is secondary to the tendency of the complex of calcium and phosphate, which comprises bone salt (presumably dahlite), to precipitate from serum when the ion product of calcium and phosphate exceeds the appropriate solubility product.

This condition would be realized in the face of the elevated serum phosphate and would explain the tendency in hypoparathyroidism for bones to be dense and for calcium to be deposited in abnormal locations.

The demineralization observed in this case might be accounted for on the basis of inadequate calcification of growing bone. Despite an elevated serum phosphate, the low serum calcium precluded a deposition of dahlite adequate for growing bone.

Treatment is based on decreasing the phosphorus intake by a diet low in phosphorus and the use of an absorptive preparation, such as an aluminum hydroxide preparation, plus a high calcium intake. The use of large doses of vitamin D_2 or dihydrotachysterol (A. T. 10) is needed. Dihydrotachysterol may act on both phosphorus excretion and calcium absorption from the gastrointestinal tract. The patient may develop a fastness to dihydrotachysterol. Calciferol acts primarily on the basis of absorption. Caution must be used to prevent overdosage. Once an overdose occurs, its effect may last about eight months before disappearing. This may result in possible kidney damage, increased calcification, and metastatic calcium deposits over the body. The calcium level should remain under 10.3 mg. per 100 cc. The Sulkowitch test should never show more than a slight to moderate turbidity.

It would be wise to start the high calcium intake several days before adding the vitamin D, so as to prevent a rapid precipitation of ionized calcium and the possible subsequent production of tetany.

SUMMARY

A case of pseudohypoparathyroidism in a 16-month-old white girl is presented.

The major manifestations of hypocalcemia, hyperphosphatemia, tetany, mental retardation, moon-shaped face, short neck, brachydactylia, strabismus, obesity, and short stature were present in this case.

The process of bone formation is reviewed.

Treatment is discussed.

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§ Dr. Herbert Jacobi, Professor of Biochemistry, University of Nebraska College of Medicine, supplied this brief summary.

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DIAGNOSIS OF ATRIAL AND VENTRICULAR SEPTAL DEFECTS

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WITH THE introduction of cardiac catheterization and angiocardiography into the diagnostic field of heart disease, more specific and exacting investigations of cardiac lesions have been accomplished. These have been associated with great strides in the surgical treatment, with the result that several of the major cardiac malformations are now amenable to surgical repair.

At present, a major focus of surgical correction is being directed toward defects in the atrial * and ventricular septa.† Since the operative indications and surgical approach are quite different, it has become important to separate the two lesions definitively, both by clinical and by laboratory methods. Although the clinical diagnosis of these lesions is often not difficult in older children and adults, it has been our experience that the differential diagnosis is often difficult in infants and in preschool children. It is our purpose to discuss the natural course of patients with ventricular and atrial septal defects and the clinical features, differential diagnosis, and laboratory diagnosis of these disorders in infancy and childhood.

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* References 1-7.

† References 8 and 9.

MATERIALS AND METHODS

1. Approximately 160 children below 21 years of age with the clinical diagnosis of ventricular septal defect and approximately 80 children with the clinical diagnosis of atrial septal defect were followed frequently by the authors in the children's cardiac clinics of the New Haven Rheumatic Fever and Cardiac Program and of the Grace-New Haven Community Hospital. Clinical experiences with this group of patients and with additional infants and children who were inpatients formed the authors' basic knowledge of these conditions.

2. A detailed review of the clinical course, physical findings, electrocardiograms, and radiologic findings of two groups of patients diagnosed as having ventricular and atrial septal defect, respectively, by cardiac catheterization was undertaken. All of these patients were examined by at least one of the authors, and the observations of physical examination, radiologic examination, and electrocardiography were standardized insofar as possible. It was recognized that these groups of patients represented an atypical sampling of patients with intracardiac defects because of the severity of the defects. The cardiac catheterizations were performed by the authors at the Grace-New Haven Community Hospital between January, 1948, and January, 1955.

Twenty of the patients studied by cardiac catheterization revealed a ventricular septal defect as evidenced by an increment in oxygen content of greater than 1 vol.% between the averaged right atrial samples and averaged right ventricle samples. None of these patients showed evidence of veno-arterial shunting of blood. This group of 20 patients included 7 patients who were in cardiac decompensation at the time of cardiac catheterization. Therefore, the group was subdivided into a group of 7 patients with ventricular defects in cardiac failure and a group of 13 patients who were well compensated.

Nine additional patients were diagnosed as having atrial septal defect by cardiac catheterization by demonstration of an increment in oxygen content of 2 vol.% or greater between the averaged vena cava samples and those of the right atrium. No anomalies of pulmonary venous return into the right atrium were present in this group as far as could be determined.

3. The proctocols of 1400 consecutive autosies performed at the Grace-New Haven Community Hospital from November, 1943, to May, 1949, were reviewed for cardiac findings. Of these, 1344 contained detailed descriptions of the intracardiac findings, including comments about the atrial and ventricular septa. Fifty-five cases (4.1%) of congenital heart disease were encountered in this group. This survey was made to assess further certain features of the intracardiac septal defects suggested by the clinical studies.

COMMON FEATURES

Certain clinical features were observed in children that were common to both ventricular and atrial septal defects and were of little aid in the diagnosis. The gracile habitus, often ascribed especially to atrial septal defects, was also observed in cases of ventricular septal defect. Precordial bulging was present in both conditions. Occurrence of transient cyanosis or slight cyanosis with exertion and crying was observed with both conditions, but more commonly with ventricular septal defects. Selzer ‡ and others have shown that there is only a difference of degree between certain ventricular septal defects and Eisenmenger's syndrome, wherein increased pressures in the right ventricle result in right-to-left shunting through the ventricular septal defect.

Diastolic murmurs were not infrequently heard in patients with either type of septal defect. An early diastolic blowing murmur was not infrequently heard in the pulmonic area and in the third and fourth left interspaces, presumably indicating insufficiency of the pulmonic valve. Also, in cases of septal defect where there was cardiomegaly, a middiastolic rumbling murmur was heard often at the apex or within this region nearer the midline. These murmurs were frequently found in the severer cases of septal defect who were referred for cardiac catheterization. Of the 13 patients with ventricular septal defect without decompensation diagnosed by cardiac catheterization by the authors, 7 showed apical or lower left sternal border rumbling middiastolic murmurs and 3 showed basilar early diastolic blowing murmurs. In the seven patients with ventricular septal defect in cardiac failure, a similar incidence of diastolic murmurs was noted, three patients showing middiastolic apical murmurs and one showing an early diastolic basilar blowing murmur. Of the nine patients with atrial septal defect diagnosed by cardiac catheterization, five showed early diastolic basilar blowing murmurs and only one a middiastolic apical rumble. Although these patients represented a small group of septal defects atypical because of their severity, it was apparent that diastolic murmurs were not uncommon with both types of septal defect [18] and that apical diastolic murmurs were often associated with ventricular septal defect. The incidence of apical rumbling murmurs in the first half of diastole associated with atrial septal defects has been higher in other series.[14]

COURSE OF VENTRICULAR SEPTAL DEFECTS

Since the original description by Roger,[15] in 1879, of ventricular septal defects, it has been well established that a significant number of patients with harsh lower-left-sternal-border systolic murmurs whose hearts are radiologically normal or minimally enlarged are asymptomatic despite the presence of ventricular septal defects. It has been apparent, however, that in many instances isolated ventricular septal defects were associated with severe symptoms and incapacity during infancy and childhood.§ Many autopsy series have revealed that this lesion, especially when it is large, is a threat to life during infancy. Edwards [19] stated, on the basis of the Mayo Clinic pathological collection, that 19 of 30 patients with isolated ventricular septal defect died before the age of 6 months. A search by us of the protocols of 1400 consecutive autopsies at the Grace-New Haven Community Hospital revealed 5 cases of isolated ventricular septal defect among 55 cases of congenital heart anomalies discovered. All of these patients died before 13 months of age. No instance of ventricular septal defect

‡ References 10-12.

§ References 16-18.

as a chance finding was revealed in the older children and adults dying of other causes in this series. Even in Maude Abbott's [20] series of 1000 autopsies of congenital cardiac lesions, 21 of 50 cases of membranous ventricular septal defects were found in patients who died before 5 years of age. The cause of death in our patients and in most of the young infants with this abnormality in the other series was cardiac failure.[18]

Among our patients, some infants with ventricular septal defect progressed well if their lesions were small, if they avoided severe respiratory infections, and if other factors, as yet unknown, were favorable. On the other hand, other infants were seriously threatened by cardiac failure in very early life and by repeated episodes of pneumonia which were associated often with cardiac decompensation. The growth and physical development were often grossly delayed. If these infants survived the first two years of life despite serious ventricular defects, often they improved surprisingly and gained somewhat on their peers in physical development. Their cardiac function and exercise tolerance improved not infrequently without digitalization. During the relatively safe childhood period, subacute bacterial endocarditis was a danger, but this becomes a greater threat with survival to adult life. When they reach adult life, these children with ventricular septal defect become subject to those factors producing left heart strain. As age progresses, these patients may be subject to hemoptyses and right-sided cardiac decompensation from persistent or increasing pulmonary hypertension and pulmonary vascular disease.‖ Some patients with ventricular septal defect who develop progressive pulmonary vascular disease will develop frank cyanosis from venoarterial shunting of blood. This transition to the Eisenmenger's syndrome has been a gradual one in our experience and has occurred more frequently in the children with ventricular septal defects who have marked pulmonary hypertension early in life.

The severity of the symptoms in infancy has been related to the location of the ventricular septal defect,[22] to its size,[13] and to the existence of pulmonary hypertension.¶

The ventricular defect has been found approximately 10 times as frequently in the membranous septum as in the muscular septum.# Defects in either of these locations have produced mild symptoms or, on the other hand, have been so severe as to produce death in infancy.[18] The lesions of the membranous septum have been more commonly associated with severe symptoms. Pulmonary hypertension was noted very early in some of these infants. Three of our cases of ventricular septal defect where the diagonsis was confirmed by cardiac catheterization before 8 months of age had extremely high pulmonary artery and right ventricular systolic pressures which approximated the systemic systolic pressures. Despite the severity of their symptoms, these patients have survived two years after their hospitalization for cardiac catheterization, have not become cyanotic, and, like many other infants with ventricular defect, have appeared to be gaining ground. Although more than 160 patients with the clinical diagnosis of ventricular septal defect have been followed by the authors in the children's cardiac clinics associated with the Grace-New Haven Community Hospital, no deaths have occurred among this group in patients over 2 years of age in the last seven years. Many cases of cardiac failure have been controlled satisfactorily with digitalization.

Because of the great threat of death in infancy and early childhood, this has become the age for focus of medical management, as well as the focus of diagnosis. Certain patients in this age range who have shown no response to medical treatment may require surgery as a life-saving measure.

‖ References 10, 12, and 21.

¶ References 12 and 18.

References 19 and 20.

CLINICAL FEATURES OF VENTRICULAR SEPTAL DEFECT

The following characteristics in children beyond infancy have proved of aid in the diagnosis of ventricular septal defect.

1. *Systolic Murmur.*—The quality, intensity, and location of the systolic murmur arising from the flow of blood through the ventricular septal defect have remained the most important and characteristic features of this disorder. This murmur was usually heard best in the fourth and fifth left interspaces parasternally and was harsh, prolonged, and extremely loud. All 20 of our catheterized cases of ventricular defect had murmurs of this character, and thrills were noted in each case. The murmur of ventricular septal defect was widely transmitted over the precordium, to the left chest posteriorly, and at times throughout the chest. Although all of our severe cases studied by cardiac catheterization revealed loud murmurs, many other patients with no symptoms also have had very loud murmurs, probably from ventricular septal defects.

In marked contrast to the usual cases of ventricular septal defect, with arteriovenous shunting only and with loud systolic murmurs, several patients with ventricular septal defect and peripheral arterial anoxemia (Eisenmenger's syndrome)[11] proved by cardiac catheterization have been observed by us to have strikingly quiet left sternal border systolic murmurs. The intensity of the systolic murmur was considered of some importance in the clinical differentiation of ventricular septal defect with arteriovenous shunting from Eisenmenger's syndrome. The intensity of the murmurs in the 20 cases of ventricular septal defect reviewed by the authors, a group excluding cases of Eisenmenger's syndrome, did not consistently vary inversely with the systolic pressure in the pulmonary artery as might have been expected.

The systolic murmur was common to all ventricular septal defects without peripheral anoxemia, was the only definite pathologic finding in some patients with minor lesions, and was the most important diagnostic feature of the disorder.

2. *Heart Sounds.*—If pulmonary hypertension was present as in severe cases of ventricular septal defect, the pulmonary second heart sound was markedly accentuated.

3. *Cardiac Impulse.*—A forceful apical thrust was often felt in cases of ventricular septal defect. This thrust may have been from an enlarged left ventricle or from the right ventricle which contracted strongly against a high pulmonary arterial pressure.

4. *Fluoroscopy and X-Ray.*—Ventricular hypertrophy was commonly noted in the severe cases. If left ventricular hypertrophy was detected, this was of great aid in distinguishing this condition from atrial septal defect, in which the left ventricle was rarely hypertrophied. Ventricular pulsation was often very strong and forceful, especially if pulmonary hypertension was present. In the severe cases, increased pulmonary vascular markings and expansile pulsations were frequently noted because of the high pulse pressure in the pulmonary artery. Nineteen of our 20 catheterized cases of ventricular septal defect showed increased pulmonary vascular markings by x-ray and fluoroscopy; 9 of the 20 showed fluoroscopic evidence of expansile pulsations of the pulmonary vessels. All of these patients showed ventricular hypertrophy by x-ray. Nineteen of the 20 cases were believed to have right ventricular hypertrophy, and 13, to have left ventricular hypertrophy. Differentiation of ventricular enlargement by x-ray was worth attempting, but it was particulary inaccurate in infants and small children.

Many of the mild cases of ventricular septal defect revealed no cardiac hypertrophy or minimal chamber enlargement which could not be differentiated.

5. *Electrocardiogram.*—The electrocardiogram quite frequently revealed no frank changes suggestive of ventricular hypertrophy, even though fluoroscopic and x-ray evidence suggested that frank ventricular hypertrophy was present. This may have reflected a similar work load for both ventricles and,

indeed, in severe cases, electrocardiographic evidence of combined ventricular hypertrophy was observed. On other occasions, right ventricular hypertrophy and right incomplete bundle-branch block patterns were visualized without evidence of left ventricular hypertrophy.

The finding of left ventricular hypertrophy by electrocardiogram, either by itself or in conjunction with right ventricular hypertrophy, aided greatly in delineating ventricular from atrial septal defects. Complete auriculoventricular dissociation patterns have not been observed in the group of approximately 160 children with ventricular septal defects in our clinics.

In cases of young severely incapacitated acyanotic infants, many of these diagnostic features were not so well defined. In these cases, the most helpful definitive diagnostic features have been the following:

1. Presence of the very loud harsh systolic murmur in the region of the fourth and fifth left interspaces parasternally. If this murmur was heard best in the fifth interspace parasternally and definitely diminished in intensity as the stethoscope was moved upward along the left sternal border above the fourth interspace, the diagnosis of ventricular septal defect was most probable.

2. Presence of a very loud pulmonary second sound, indicating pulmonary hypertension.

3. Presence of left ventricular hypertrophy or of combined ventricular hypertrophy either by electrocardiogram or radiologically.

Without the presence of a typical murmur, the diagnosis was very difficult and often it was made only after cardiac catheterization in the infant age group.

COURSE OF ATRIAL SEPTAL DEFECT

Atrial septal defect * as an isolated lesion must be separated from the lesions of atrial septal defect in association with anomalous pulmonary venous drainage into the right atrium † and from the anomaly of atrioventricular canal.‡ The atrial septal defects must also be separated insofar as possible into those involving defective closure of the foramen ovale and defects in the septum on the one hand and the severer lesion of persistence of the ostium primum on the other hand. In the latter condition a large defect of the lower portion of the atrial septum is present and the medial leaflet of the mitral valve is often deformed. The lesion of atrioventricular canal involves persistence of the ostium primum, but in addition it involves defective formation of the mitral and tricuspid valves and a membranous ventricular septal defect. In the discussion to follow, "atrial septal defect" will be defined as a defect of the atrial septum alone. Cases of persistence of the ostium primum with right-to-left shunting or with mitral valvular dysfunction are excluded from this group. Because the lesion of persistent ostium primum is intermediary between that of isolated atrial septal defect and the combined atrial and ventricular septal defect of atrioventricular canal, this lesion will be discussed separately in the differential diagnosis.

Small atrial septal defects may be asymptomatic throughout life. An opening of 0.5 cm. in diameter permitting free flow of blood from left to right atrium might be expected to produce symptoms and signs, but the lesions causing great difficulty are usually considerably larger. The size of the mitral valve may be important in the degree of shunting from left to right atrium. If the mitral valve is relatively small or if congenital mitral stenosis is present, shunting will be considerable and the left ventricle and aorta usually will be small. The diminished left heart output may be associated with slow growth and the "gracile habitus."

Except in instances of extremely large defects, those patients under our care with isolated atrial septal defect were under less threat than many of the patients with ventricular septal defects during infancy. They

* References 23-26.

† References 27-29.

‡ References 30 and 31.

were subject, however, to repeated episodes of pneumonia. The usual absence of pulmonary hypertension in these cases was a favorable factor.

Atrial septal defect was at times quite benign, and such cases often were not referred to our clinics until school age. On the other hand, patients with atrial septal defect more so than those with ventricular septal defect have been said to be in danger of developing rheumatic endocardial lesions during childhood.§ Patients with marked atrial enlargement have been said to be particularly prone to develop cardiac irregularities such as atrial fibrillation and flutter, although these usually do not develop until late childhood or adult life. Since patients with atrial septal defects usually survive infancy, the diagnosis and surgical management can be focused on the childhood period.

CLINICAL FEATURES OF ATRIAL SEPTAL DEFECT

In older children the diagnosis of atrial septal defect was not usually difficult, but in infants and younger children more difficulties arose. Those criteria which have been of greatest aid to the authors in the diagnosis include the following:

1. *Systolic Murmur.*—The systolic murmur of atrial septal defect was usually of moderate intensity and softer than that of ventricular septal defect. It was usually best heard in the second and third left interspaces parasternally and was often transmitted high posteriorly. Because of its similarity to the murmur of valvular pulmonary stenosis, this murmur has been said to originate from the relative pulmonary stenosis caused by the increased flow of blood through the normal pulmonary valve. A second or third left interspace systolic thrill was present not infrequently and was noted in six of the nine cases of atrial septal defect studied by cardiac catheterization by us. The absence of a thrill was of some diagnostic importance, since this rarely occurred in ventricular septal defect, but the subjectivity of palpation of thrills must be acknowledged.

2. *Pulse Pressure.*—The peripheral pulse has been said to be small and the pulse pressure narrow if hypoplasia of the aorta exists.[17] This sign has not proved of great value in children.

3. *Cardiac Impulse.*—A slapping cardiac impulse was usually noted in cases of atrial septal defect, with the point of maximal impulse within the left border of cardiac dullness and the apical area.

4. *Heart Sounds.*—The pulmonic second sound was often widely split and was usually of normal intensity. The impurity of the sound reflected asynchronous pulmonary and aortic valve closure which has been said to be caused by asynchronous emptying of the large right and small left ventricle.[17] Pulmonary hypertension, which was unusual in children with atrial septal defect, resulted in accentuation of P_2.

5. *Fluoroscopy and X-Ray.*—Findings on fluoroscopy have included right ventricular hypertrophy, prominence of the pulmonary conus, and increase in pulmonary vascular markings. All nine of our cases of atrial septal defect confirmed by cardiac catheterization showed increased pulmonary vascular markings; four showed expansile pulsations; seven had right ventricular hypertrophy by x-ray. A small aortic knob or evidence of hypoplastic aorta was difficult to evaluate and was ascertained only in several of our patients in whom large shunts were evident.

6. *Electrocardiogram.*—It has become increasingly apparent that the findings of right bundle-branch-block patterns, either complete or, as is commonest, incomplete, is an important diagnostic feature of atrial septal defect.‖ Incomplete right bundle-branch-block or right ventricular hypertrophy patterns were seen in the great majority of our patients diagnosed as having atrial septal defect and were observed in all of the patients studied by cardiac catheterization. Normal axis or right axis deviation was usually ob-

§ References 32-34.

‖ References 16 and 17.

served. Irregularities of auricular conduction, such as auricular flutter and fibrillation, have developed in cases of atrial septal defect in adults, especially where a small or stenotic mitral valve has increased the degree of atrial hypertrophy. The only patient below 10 years of age among the approximately 80 cases of atrial septal defect under observation at our cardiac clinics who was observed to develop auricular fibrillation was receiving a digitalis dosage possibly in the toxic range and improved when the digitalis dose was lowered.

Instances of progressive cardiac decompensation and death during infancy due to atrial septal defect have been unusual, but they have been reported.[35] No case of this type was noted among the 1400 consecutive autopsies reviewed by us. As with ventricular septal defect, some of the infants with large atrial septal defects have improved after surviving the first two years.

In contrast to the infants with very large atrial septal defects, some of those with a small defect appeared normal and had no symptoms suggestive of heart disease. The diagnosis was not established easily in these patients, who often showed moderate systolic murmurs in the region of the third left interspace transmitted into the upper left chest posteriorly, right incomplete bundle-branch-block patterns on electrocardiogram, and splitting of the pulmonic second sound as the only abnormal findings.

DIFFERENTIAL DIAGNOSIS

While we have encountered difficulty in differentiating the ventricular and atrial septal defects one from another, likewise we have had difficulty in clinically distinguishing these lesions from other cardiac abnormalities.

The most difficult lesions to differentiate from the isolated septal defects have been (1) combined septal defects, including atrioventricular canal; (2) persistent ostium primum with right-to-left shunting of moderate degree and deformity of the mitral valve; (3) anomalies of pulmonary venous return to the right atrium, and (4) atypical patent ductus arteriosus. Other malformations which have been difficult to distinguish from the septal defects on occasion have been (5) isolated pulmonary stenosis, (6) mitral stenosis, (7) valvular aortic stenosis, (8) subendocardial fibroelastosis, and (9) some lesions with cyanosis in infants. (10) Functional murmurs have been difficult to differentiate from the mild septal defects occasionally.

1. *Combined Septal Defects.*—Atrial and ventricular septal defects have been noted in the same patient not infrequently. Two such cases were observed in infants dying before 4 months of age among the 55 autopsies reviewed by us, and another such case was observed in a child who died recently on our cardiac service. The septal defects in these patients were separated by intact septum and did not represent the lesion of an atrioventricular canal wherein the tricuspid and mitral valves are involved in a large septal defect of the lower atrial and membranous ventricular septum. Atrioventricular canal has produced certain signs, including a very harsh long systolic murmur, loudest in the third and fourth left interspaces; slight cyanosis at times, and an electrocardiogram with left axis deviation or indeterminate axis in association with right ventricular hypertrophy, which have aided in the differentiation from isolated septal defects. The murmur has been more harsh than that of atrial septal defect, and its location has been higher at times than that of ventricular defect. The electrocardiographic picture described has not always been present and may be noted rarely in cases of ventricular septal defect. The combined septal defects have produced less specific signs. Where the ventricular septal defect was the severer lesion, the signs produced obscured the presence of the atrial defect. Although we have not observed the abnormality where the predominant atrial defect obscured a less severe ventricular septal defect, this might also occur. With our present knowledge we have been unable usually to distinguish these combined ventricular and atrial septal defects from the isolated lesions clinically.

2. *Persistent Ostium Primum with Right-to-Left Shunting and Deformity of the Mitral Valve.*—This abnormality has produced signs similar to those of atrioventricular canal, including a third and fourth left interspace murmur which fills systole, and the electrocardiographic picture of left axis deviation or indeterminate axis in association with right ventricular hypertrophy. As in atrioventricular canal, this lesion results from a very early developmental abnormality and often has been associated with other major congenital abnormalities. Persistence of the ostium primum where right-to-left shunting of blood was minimal and where the mitral valve functioned adequately could not be excluded from the other forms of atrial septal defect.

3. *Anomalies of Pulmonary Venous Return into the Right Auricle.*—The anomalies of pulmonary venous return usually have not been difficult to differentiate from ventricular septal defect, but they have produced a clinical picture at times indistinguishable from atrial septal defect.¶ In those patients in which anomalous pulmonary venous drainage into the right atrium has occurred, atrial septal defects frequently have been present. Detection of this combination of lesions has not been possible without resort to cardiac catheterization and dye-dilution techniques. When pulmonary venous return has been to the superior vena cava, a prominent bulge has been observed radiographically in the region of the superior vena cava,[36] producing a so-called "snow man" appearance of the cardiac contour. We have observed, as have others, the presence of a continuous murmur in the region of the second right interspace in patients with this malformation.

Complete anomalies of pulmonary venous return [37] which have been characterized by return of all the pulmonary blood to the right atrium have been difficult to distinguish from large isolated atrial septal defects, especially during the infancy period. These lesions have been accompanied by the presence of atrial septal defects which allow blood to pass from right to left atrium and are associated with anoxemia. Death caused by the anomaly of complete pulmonary venous drainage into the right circulation has occurred early in life, usually during the first year. Survival beyond this age and the absence of cyanosis have argued strongly against the presence of this anomaly.

4. *Atypical Patent Ductus Arteriosus.*—In infancy, patent ductus arteriosus # has been featured by a prolonged systolic murmur at the base of the heart with no diastolic component. The maximum point of intensity of this murmur has often been at a lower point than that usually observed in older children. Patients with this type of bruit who have shown cardiomegaly, increased pulmonary vascular markings by x-ray, poor physical development, and recurrent respiratory infections often could not be clinically distinguished from patients with severe atrial or ventricular septal defects.

During childhood, atypical murmurs [40] have been observed in patients with patent ductus arteriosus and pulmonary hypertension.* These murmurs have been indistinguishable from the basilar murmurs of atrial and ventricular septal defect. Resort to cardiac catheterization and retrograde aortography has been necessary for diagnosis. The combined malformations of patent ductus arteriosus with ventricular septal defect and patent ductus with atrial septal defect have been found not infrequently.

Aorticopulmonary septal defect has simulated large patent ductus arteriosus † and has been difficult to differentiate from the septal defects when the continuous murmur was absent.

5. *Isolated Pulmonary Stenosis.*—The most important differential feature between isolated pulmonary stenosis and atrial septal defect has been the quality and intensity of the second sound. We have found that exercise may accentuate the split, moderately loud pulmonic second sound of atrial septal de-

¶ References 27-29 and 36.

References 38 and 39.

* References 41-46.

† References 47-49.

fect while not affecting the soft second sound of pulmonary stenosis in patients where question has been raised about this important differential diagnostic sign. The systolic murmur of pulmonary stenosis has been said to be transmitted better to the shoulder than that of atrial septal defect.

6. *Mitral Stenosis.*—Because of the frequency of mitral diastolic murmurs in patients with atrial septal defect, this malformation has been difficult on rare occasions to distinguish from congenital mitral stenosis or from rheumatic mitral stenosis. The lesion of mitral stenosis, congenital or acquired, has been associated with atrial septal defect as the Lutembacher syndrome, but in children this syndrome has not been very common.[13]

7. *Aortic Stenosis.* — Congenital aortic stenosis, particularly valvular stenosis in infants, has been difficult to distinguish from ventricular septal defect unless maximum intensity of the aortic murmur can be properly localized at the aortic area and upper midsternum.

8. *Subendocardial Fibroelastosis.*—Infants with this condition.‡ which primarily involves the endocardium of the left ventricle and may distort the mitral and aortic valves, have shown a variety of cardiac murmurs and often have developed progressive cardiac decompensation. These findings associated with electrocardiographic changes which have resembled those of left ventricular hypertrophy have occasionally made differentiation from ventricular septal defect difficult during infancy.

9. *Cyanosis in Infants.*—Although anoxemia has been present, cyanosis was difficult to observe in some of the infants with the less severe congenital malformations with venoarterial shunting. A common misdiagnosis during infancy has been that of ventricular septal defect for tetralogy of Fallot. Demonstration of anoxemia and appearance of cyanosis in association with the other classical features of tetralogy of Fallot has clarified the diagnosis in these patients.

10. *Functional Murmurs.* — During infancy, functional murmurs have been repeatedly observed by us to have greater intensity and harshness and better transmission through the infant's thin chest than the functional murmurs observed in older children. Therefore, the functional murmurs of infancy have been suggestive of the murmurs of atrial and ventricular septal defect. Serial observations of these murmurs have revealed gradual evolution into the classical functional murmurs of childhood or disappearance of the murmurs entirely. In our experience the commonest functional murmur of childhood has been a vibrant, harsh, somewhat humming murmur usually maximal in the fourth left interspace near the sternum. This murmur, variable with position and exercise, has been transmitted often to the apical region and up along the left sternal border to the neck. A second less common systolic functional murmur has been a basilar blowing murmur which has often been associated with a venous hum. The variability and lack of posterior transmission of this latter murmur has differentiated it from the murmur of atrial septal defect.

LABORATORY DIAGNOSIS BY SPECIAL TECHNIQUES

The techniques of cardiac catheterization, dye-dilution curves,[54] angiocardiography,§ and retrograde aortography[57] have been widely used in an attempt to diagnose arteriovenous shunts accurately.

Cardiac Catheterization.—This technique has been easily and quite safely carried out in adults and older children, but as the younger age ranges have been approached the difficulty and danger have risen. In our experience, in infants less than one year of age the catheter was best introduced into the saphenous vein, because the possibility of air embolism was greater when the introduction was made through the other readily accessible vein, the external jugular. When the catheter was introduced through the saphenous vein, intracardiac manipulation was dif-

‡ References 50-53.

§ References 55 and 56.

ficult at times, and quite often the pulmonary artery was not entered readily. On almost all occasions, the right ventricle was readily sampled, as was the right atrium, the superior vena cava, and the inferior vena cava. The mortality due to cardiac catheterization of infants below one year of age has been approximately 1.7% in the most experienced hands.[58]

The diagnosis of a septal defect was made in two ways: (1) the catheter was passed through the septal defect, or (2) a significant increase in oxygen saturation was demonstrated with the catheter tip near the arteriovenous shunt.

On occasions, during cardiac catheterizations not included in this report, the catheter appeared to pass from the right to the left atrium when it was actually passing into an anomalous pulmonary vein emptying into the right atrium. At other times, the catheter was passed from right atrium to left via a small patent foramen ovale by pushing back the valve of the foramen. Therefore, we have placed most credence in the demonstration of the increment in saturation between vena cava and right atrium in the diagnosis of atrial septal defect. Passage of the catheter tip through a ventricular septal defect into the left ventricle was not detected by us in the cases reported and has been difficult to detect fluoroscopically. Passage into the left ventricle and promptly into the aorta was readily noted in several patients with Eisenmenger's syndrome, but it was not observed in any of the patients with ventricular septal defect included in this report.

With use of these criteria, the diagnosis of the particular septal defect could usually be made by cardiac catheterization even in the infant age group. In certain cases where because of technical difficulties not all of the desired information was obtained, the diagnosis was still doubtful even after the cardiac catheterization. When combined atrial and ventricular septal defects were present, the defect producing the greater shunt infrequently obscured that producing the lesser.

Dye-Dilution Curves.—The lesion of abnormality of pulmonary venous return wherein only part of the pulmonary blood was returned to the right atrium was difficult to distinguish by cardiac catheterization from atrial septal defect. Often anomalies of pulmonary venous return occurred in association with atrial septal defects. From the standpoint of circulatory dynamics these lesions were quite similar. The use of T-1824 dye-dilution curves registered by earpiece or cuvette oximetry after dye has been introduced into the right and left pulmonary arteries, respectively, has revealed curves with different characteristics depending on the drainage of the right and left pulmonary veins.[59]

The proportion of blood draining from the right and left pulmonary veins into the left and right auricles can be estimated by this technique. In the absence of cyanosis, anomalous pulmonary venous drainage will rarely result in a left-to-right shunting of blood greater than half the left cardiac output. If shunts larger than this are calculated by the Fick principle from cardiac catheterization data, the presence of an atrial septal defect is most likely.

Swan and co-workers [60] have shown also that injection of T-1824 into the inferior vena cava in many patients with atrial septal defect will result in appreciable right-to-left shunting of blood. Since in infancy the foramen ovale lies opposite to the entry of the inferior vena cava, right-to-left shunting might be expected, especially in this age range when atrial septal defects are present. This correlates with our observation that slight cyanosis has been occasionally present in infants with atrial septal defect who later revealed no demonstrable anoxemia.

Angiocardiography.—Lind and Wegelius [58] have shown recently that injection of radio-opaque dye into the saphenous vein under pressure resulted in right-to-left shunting of dye-containing blood through atrial septal defects. The consistent demonstration of this shunting required the use of complex rapid-changing x-ray equipment. One might have expected that reflux of dye into abnormal pulmonary veins entering the right atrium might also have been demonstrated

by this technique. Using a two-per-second x-ray changer with rapid dye injection through a catheter in the right atrium, we have not been able as yet to visualize an atrial defect where this probably existed as the only lesion.

The most promising technique for visualization of abnormalities of pulmonary venous return may be the use of angiocardiography with separate injections of radio-opaque material through the catheter placed in the right and later in the left pulmonary arteries.

Retrograde Aortography. — Retrograde aortography [67] consists of the injection of 35% iodopyracet (Diodrast) or similar material intra-arterially in such a way that the aorta may be outlined on films taken at rapid intervals. The aortograms have aided in the differential diagnosis of patent ductus and the intracardiac septal defects by revealing the presence of a patent ductus arteriosus by passage of the radio-opaque material from the aorta to the pulmonary artery.

SUMMARY

The course, clinical features, differential diagnosis, and laboratory diagnosis of isolated ventricular and isolated atrial septal defects in infants and children are discussed with reference to our experiences.

Clinical diagnostic criteria for these lesions as they are presented in infants and children are enumerated.

Dr. Mary Thornton, Dr. Peter LaForte, Miss Dorothy Nixon, Miss Theresa D'Ambrosi, Mrs. Augusta Vandervliet, and Miss Norma Neilson gave technical assistance in this study.

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Correspondence

OVERDOSAGE OF VITAMIN K

To the Editor: A warning needs to be given to pediatricians and obstetricians about using unduly large doses of any water-soluble vitamin K preparation in premature infants. Communications (appearing in Letters to the Editor, *Lancet* **1**:669 [March 26]; 819 [April 16] 1955) report fatal hemolytic anemia occurring in two small series of infants. The vitamin K was given in one or more doses of 10 mg. to these premature infants. No evidence of blood-group incompatibility or Rh-factor problem was found.

A further report appeared (Letters to the Editor, *Lancet* **1**:819 [April 16] 1955) in substantiation of the hemolytic effect of very large doses (100 mg/kg.) of water-soluble vitamin K given to rats. This hemolysis occurred only in rats deprived of vitamin E. It is known (Rose, C. S., and György, P.: *Blood* **5**:1062 [Nov.] 1950) that vitamin E deficiency in rats leads to abnormaly great hemolytic tendency. Recent work, as yet unpublished, has confirmed this for adult humans. It has been reported (Dju, M. Y.; Mason, K. E., and Filer, L. J., Jr.: Études néo-natal. **1**:49 [Sept.] 1952) that the human fetus and infant tend to have small amounts of vitamin E in tissues.

The dose of vitamin K which is adequate when given antepartum for prevention of hemorrhagic disease in the newborn is usually thought to be 1 mg. Parenteral administration of 5 mg. to infants has had wide use and without hazard being reported, even in premature infants (Letters to the Editor, *Lancet* **1**:819 [April 16] 1955). Too frequently, physicians have assumed that great overdosage of vitamins is innocuous. This is unwise, especially so far as parenteral administration of thiamine or nicotinic acid (niacin) is concerned. The recent reports draw attention to upper limits for water-soluble vitamin K, at least in premature infants. There is no reason to fear harm from the long-established dosage range up to 5 mg. Neither is there any reason to use a much larger dosage. No unfavorable reports have appeared concerning oral use of the water-soluble vitamin K.

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Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

PATHOLOGIC CHANGES ASSOCIATED WITH THE USE OF SODIUM ETHYLENE DIAMINE TETRA-ACETATE IN THE TREATMENT OF HYPERCALCEMIA. H. R. DUDLEY, A. C. RICHIE, A. SCHILLING, and W. H. BAKER, New England J. Med. **252**:331 (March 3) 1955.

Two cases of hypercalcemia treated with sodium ethylenediamine-tetraacetate are described. One patient was a woman dying with osteolytic metastases, and the other a child with acute hypercalcemia after vitamin D therapy.

In both cases there was the same combination of three unexpected findings at autopsy: severe damage to the renal tubules, engorgement of the reticuloendothelial cells with coarse eosinophilic granules, and hemorrhagic manifestations.

Reason is given for thinking that these lesions may have been due to the administration of the drug. The clinical use of sodium and calcium ethylenediamine-tetraacetate is discussed.

FROM THE AUTHORS' SUMMARY.

ALIMENTARY NITRATE METHEMOGLOBINEMIA IN EARLY INFANCY. T. BODÓ, Monatsschr. Kinderh. **103**:8-12 (Jan.) 1955.

The author reported seven cases of methemoglobinemia in infants ranging in ages from 2 to 10 weeks. Clinical findings consisted of cyanosis, tachycardia, diarrhea, and marked irritability. All patients had been receiving well water as part of their fluid intake (either in the preparation of their formulas or with tea). Nitrate content of the well water ranged from 56 to 1100 mg/liter. Photometric study of the blood was performed in six patients and was positive for methemoglobin in every instance. Arterial oxygen saturation studies performed in three infants were 50%, 59%, and 65%.

Duodenal contents of these infants were examined and revealed nitrate-splitting (nitrite-forming) coliform bacteria in all cases except one. Gastric contents were examined for pH in six cases, which was found to be 5.00 in three instances, 2.5, 3.5, and 4.5 in the remaining cases.

Treatment with 1% methylene blue solution (1 mg/kg.), either intravenously or rectally, cleared the cyanosis within 20-30 minutes in all patients, and there were no deaths in this series.

It was concluded that hemoglobin of young infants was easily oxidized and that when infants are receiving water with a high nitrate content, they are prone to develop methemoglobinemia, as nitrate-splitting (nitrite-forming) coliform organisms are present in the gastrointestinal tract.

HARTENSTEIN, Syracuse, N. Y.

AMINOACIDURIA IN TUBERCULOUS CHILDREN AND ADOLESCENTS. HEINZ KLEINBAUM, Monatsschr. Kinderh. **103**:26-28 (Jan.) 1955.

Urinary paper chromatography of healthy and tuberculous children revealed the following findings:

1. Normal children excreted a variety of amino acids in varying amounts.

2. Every patient with skeletal tuberculosis excreted valine, whereas only 15% of healthy controls excreted valine.

3. Arginine and threonine were never found in normal children.

4. Children with chronic pulmonary tuberculosis with cavitation excreted valine and arginine in large amounts.

5. This was thought to be characteristic of the increased protein breakdown which is present in chronic tuberculosis.

6. It was postulated that arginine may be poorly reabsorbed by the renal tubules in the presence of increased blood amino acid levels.

HARTENSTEIN, Syracuse, N. Y.

Prematurity and Congenital Deformities

LEPRECHAUNISM. W. L. DONOHUE and IRENE UCHIDA, J. Pediat. **45**:505-519 (Nov.) 1954.

Donohue and Uchida report the case of two baby girls in the same family born with the little wizened hairy look of leprechauns. Their Anglo-Saxon parents are first cousins once removed and apparently healthy. The first leprechaun was their firstborn, then there were two successive pregnancies that ended in abortion, then a girl, and after her a boy, both perfectly normal. After the boy there was a pregnancy that ended in miscarriage and then, the seventh pregnancy, another leprechaun.

These two infants were small, about the size of a seven-month fetus—the mother said that they seemed to stop growing after the seventh month of pregnancy. Both showed hypertrophy of the breast and clitoris. Both developed subcutaneous abscesses, and both died under the age of 3 months.

Autopsy findings were similar. There was hyperplasia in the ovaries and pancreas and possibly the thymus and pituitary. There was hypertrophy and calcinosis of the kidneys. The adrenals were normal. But there were abnormal deposits of glycogen and iron in the liver.

The authors suggest that the syndrome is probably the homozygous combination of a rare recessive gene facilitated by the consanguinity of the parents.

It is a pity that there must be leprechauns like this but, if they must be, it is only right and proper that a Donohue should be the one to describe them.

MACDONALD, Pittsburgh.

THE EFFECT OF COBALT AND IRON SALTS ON THE ANAEMIA OF PREMATURITY. B. L. COLES and URSULA JAMES, Arch. Dis. Childhood **29**:85 (April) 1954.

Cobalt appears to be of value in the prevention of the early anemia of premature infants, and if iron is administered simultaneously the risk of an iron deficiency anemia developing from the fourth month onward is considerably reduced. Cobalt has no toxic effects and no unfavorable influence on the weight gain in the dosage employed. The mode of action is uncertain, but two possibilities seem likely: (1) a direct action on the erythropoietic tissue in the marrow; (2) a possible catalytic action enabling available iron to be utilized more readily for hemoglobin synthesis.

KELLY, Milwaukee.

THE VALUE OF HUMAN MILK COMPARED WITH OTHER FEEDS FOR PREMATURE INFANTS. V. MARY CROSSE, EVELYN M. HICKMANS, BETTY E. HOWARTH, and JOAN AUBREY, Arch. Dis. Childhood **29**:178 (June) 1954.

The authors cannot subscribe to the opinion of those who state that human milk is unsuitable or inferior for premature babies. It is the food which is best tolerated by the smallest babies during the first few weeks of life and by sick premature babies. The return to the birth weight is not prolonged, and the subsequent weight curves run parallel to the in utero curve if sufficient calories are given (60 per lb. [450 gm.] daily). There is no evidence to show that anemia or hypoproteinemia are commoner among infants fed on human milk than on high-protein diets. The incidence of infection and mortality are lowest among those fed on this natural food.

There is no doubt that the half-skimmed dried milk mixture produces a more rapid gain in weight during the first six to eight weeks of life, but there is good reason to believe that this is mainly due to increased water retention and not true growth. If human milk cannot be obtained, half-skimmed dried milk is a fairly good substitute.

KELLY, Milwaukee.

APHONIA IN CONGENITAL ANOMALIES. OTTO TEZNER, Ann. pædiat. **183**:332 (Dec.) 1954.

Aphonia was observed during crying in three newborn babies with congenital heart anomalies of various types. This is due to a paresis of the left recurrent nerve. Aphonia observed in newborn children during crying should draw attention to the presence of a possible vitium cordis.

FROM THE AUTHOR'S SUMMARY.

ETIOLOGY, PATHOGENESIS AND PROPHYLAXIS OF RETROLENTAL FIBROPLASIA. T. BREHME, Schweiz. med. Wchnschr. **85**:302 (March 26) 1955.

It is recognized that a too high concentration of O_2 over a long period of time in the incubator is the main factor in the initiation of retrolental fibroplasia. The retina is distinguished

by a high anaerobic glycolysis, which is inhibited by exposing the premature infant to high O_2 concentration. A contraction of the arterial vessels of the retina not yet completely vascularized in premature infants below 1900 gm. is the response to the hyperoxia which is the first stage of retrolental fibroplasia. This contraction interferes with the nutrition of the retina and so with its further development. On return to normal atmosphere, a primitive nondifferentiated vascularization with formation of connective tissue takes place as second and third phases of the disease as relative hypoxic retinopathy with disturbance of the usual development of the retina. Retrolental fibroplasia can be prevented by drastic reduction of O_2 in the incubator.

AMBERG, Rochester, Minn.

PREMATURITY AT PROVINCIAL MATERNITY HOSPITAL IN BARCELONA. ELISARDO MARTINEZ CARMONA, Rev. españ. pediat. **10**:15-26 (Jan.-Feb.) 1954.

A study of the causes and contributing factors of prematurity in the Maternity Hospital at Barcelona was made. There were 2162 cases among 27,911 births. The etiology of prematurity was known in 50.22% of the cases. Total mortality was 28.02%.

This study was made on all cases from 1916 to 1952; the percentage of premature births in 1916 was 12.1%. In 1952 it was 9.2%, a fall in rate which the author does not consider significant.

The age of the mother, number of children of the mother, her health, incidence of twins, congenital defects of children, and weight of babies are among the factors studied.

ALLEN, Santa Fe, N. Mex.

SOME ASPECTS OF PREMATURITY AND THE METHODS OF PREVENTION. J. L. MATA CARREROS, Rev. españ. pediat. **10**:45-64 (Jan.-Feb.) 1954.

The author first discusses the medical problem related to premature infants then outlines a prevention program which includes (1) education, both medical and for the general public; (2) more careful statistical studies; (3) research in medical centers, especially in the departments of obstetrics and pediatrics; (4) prophylaxis; (5) coordination of all services, such as public health, civil registry, medical colleges, and private hospitals; (6) assistance or welfare organizations.

ALLEN, Santa Fe, N. Mex.

ARTIFICIAL HIBERNATION: ITS APPLICATION IN THE PREMATURE. JORGE BEATO NUNEZ, RENE MONTERO, and CARLOS M. MONTALVO, Arch. med. inf. **23**:285 (Oct.-Dec.) 1954.

Artificial hibernation, a procedure conceived by Laborit and Huguenar, of Paris, is a pharmacodynamic procedure which, by the combination of several vegetativolytic drugs, aims at obtaining controlled inhibition of the neurovegetative system, and thereby a weakening or reduction of homeostatic reactions.

By avoiding the organic reaction to aggresion, through vegetative disconnection, we try to spare the energy of the patient in order to prevent exhaustion, while employing any therapeutic measures desired at this time.

Thus, neurovegetative disruption is achieved by the use of a series of derivatives of phenothiazine, which, by the order of their efficacy, are Largectil, Fenergan, and Dipareol. All of these are, at the same time, acteylcholinolytic, sympatholytic, and histaminolytic, while each shows a predominance of one of these effects. Moreover, Largectil has some effect on the diencephalon and, according to some authors, inhibits the impulses from the cerebral cortex to the diencephalon.

After the disconnection of the neurovegetative system, general refrigeration may be employed for the purpose of reducing cell combustion. In an individual whose homeostatic reactions are inhibited by the interruption of the neurovegetative pathway, low temperatures will lose their aggressiveness under normal conditions, and are, on the contrary, liable to exert a favorable action by impeding tissue anoxia, the main cause of shock.

Artificial hibernation is no etiological treatment, but it is a most valuable means for facilitating a procedure for slowing down the evolution of a pathologic condition, thus procuring some rest, which will permit the organism to economize its resources while the decisive fight with the disease is being organized, in which our whole modern therapeutic arsenal is used.

The neurovegetative system of the premature child is not developed sufficiently for maintaining homeostasis when exposed to the inevitable aggressions from outside, therefore its

efforts to maintain, at the same time, thermogenesis, tissue vitality, and growth suggest an exaggeration of its metabolic activity, liable to lead to exhaustion of its resources. When considering the spontaneous hypothermia of premature infants as a physiologically defensive attitude, directed against the crisis of birth and the adaptation to life, to air, and, in view of their chronic anoxia, to artificial hibernation, in the treatment of these infants, according to the concepts of Laborit, it is particularly indicated.

FROM THE AUTHORS' SUMMARY.

CRANIOTABES IN PREMATURE INFANTS. W. JUNG, Monatsschr. Kinderh. **102**:224-227 (April) 1954.

One hundred fifteen premature infants, ranging in birth weights from 1080 to 2400 gm., were divided into four groups.

Patients in Group I received weak continuous ultraviolet irradiation and 600 to 4000 units of vitamin D_3 in emulsion daily. Of the 36 patients in this group, 26 developed craniotabes.

Patients in Group II received stronger ultraviolet irradiation and 6000 units of vitamin D_3 emulsion daily in five divided doses. None of the 36 patients in this group developed craniotabes.

Patients in Group III received the same strength ultraviolet irradiation as those in Group II and 6000 units of vitamin D_2 emulsion in three divided doses daily. Of the 18 children in this group, 5 developed craniotabes.

Patients in Group IV did not receive any vitamin D preparation but only strong ultraviolet irradiation. Of the 25 patients in this group five developed craniotabes.

The author concluded that a combination of ultraviolet irradiation and prolonged daily vitamin D administration prevents the development of craniotabes. It was, furthermore, clear that craniotabes in premature infants represents a sign of rickets.

HARTENSTEIN, Syracuse, N. Y.

INTRAUTERINE INFECTION OF THE FETUS. C. B. F. DAAMEN, Nederl. tijdschr. geneesk. **98**:666 (March 13) 1954.

In 255 infants who died perinatally, the umbilicus was examined for signs of infection. As could be expected, a slight inflammatory reaction with leucocytes as a sign of the demarcation of the umbilicus was found in 43 of 49 infants who had lived for longer than one day. The reaction with leucocytes, however, was also seen in 17 of 81 stillborn infants. In this latter group of infants other signs of infection were also found: pneumonia seven times, membranitis in the placenta six times. This membranitis is most probably caused by infection of the fetus. At least in 9 of these 17 cases the membranes had ruptured longer than 24 hours before the birth of the child. Six times the mother herself showed signs of infection. It is improbable that the above-mentioned reaction of leucocytes is caused by intrauterine anoxemia, because of the fact that so often in cases of anoxemia no reaction appears. It is advised to give antibiotics prophylactically in case of premature rupture of the membranes.

VAN CREVELD, Amsterdam.

Acute Contagious Diseases

THE SINGLE APPROACH TO STREPTOCOCCIC PROPHYLAXIS. ROBERT A. TIDWELL, Northwest Med. **54**:467 (May) 1955.

The author presents the results of a small controlled study carried out in the home to determine the efficacy of a long-term prophylactic program using daily oral doses of benzathine penicillin for control of streptococcal upper respiratory infections in rheumatic and cardiac patients and in their family contacts. The results were most favorable.

DOCTER, Seattle.

VACCINATION AGAINST SMALLPOX AND FOLLOWING POLIOMYELITIS. R. SIEGERT, Schweiz. med. Wchnschr. **85**:329 (April 2) 1955.

Revaccination against smallpox was performed on 330 twelve-year-old children, shortly before the beginning of a wave of poliomyelitis. Two children acquired poliomyelitis on the 31st and 33d days, and one on the 54th day, all with severe paralytic manifestations. In three cases the left arm, which had been used for vaccination, was not affected, and in the fourth case

the transitory paralysis was less severe in the left arm than the other extremities. The frequency of poliomyelitis in the vaccinated children was not beyond that of nonvaccinated children.

It is not possible to establish a relationship between the poliomyelitis and the preceding revaccination.

AMBERG, Rochester, Minn.

FUNDAMENTAL CONSIDERATIONS WITH REGARD TO THE ACTIVE IMMUNIZATION AGAINST POLIOMYELITIS. R. HAAS, W. KELLER, and W. KIKUTH, Deutsche med. Wchnschr. **80**:273 (Feb. 25) 1955.

This paper reviews the problem of immunization against poliomyelitis with attenuated virus, including oral administration and the procedure of Salk, stressing the testing of the vaccine prepared by the Behring Laboratory. More than 1000 persons including over 500 children have been vaccinated. The vaccination was tolerated very well.

AMBERG, Rochester, Minn.

THE CLINICAL PICTURE OF HERPANGINA. A. WINDORFER and H. SCHRICKER, Deutsche med. Wchnschr. **80**:369 (March 18) 1955.

The disease starts acutely with high fever, and occasionally convulsions occur. The general symptoms are those of an acute infection. Pain on deglutition points to the important herpes-like lesions in the posterior part of the buccal cavity. The duration is five days, the fever lasting one to four days. The disease is seen preponderantly in children. In a period of four years, 14 boys and 19 girls were observed. Of these, 11 were infants below 1 year of age and 11 were 1 to 3 years of age. The fever varied between 38.5 and 40 C (101.3 and 104 F). The blood picture is not characteristic. One child with symptoms of meningitis had normal spinal fluid. Recurrences were seen in three instances three to five weeks after the first attack. In a 2-year-old boy, a Coxsackie virus could be demonstrated on animal inoculation. In nine other cases this was not possible. Four of 16 serological examinations showed titer of over 1:16 with Type A_2. A titer of 1:10 is regarded as proof. The serological test requires some time to become positive. The differential diagnosis is discussed. Coxsackie virus A is held responsible for this disease, while Virus B is responsible for Bornholm disease. Herpangina is regarded as a disease entity which can occur in connection with other infectious diseases, such as exanthema subitum, measles, bronchopneumonia, and scarlet fever. The prognosis is good, but exceptions seem possible. There is no specific therapy.

AMBERG, Rochester, Minn.

TREATMENT OF CHILDHOOD TUBERCULOSIS WITH ISONIAZID. W. PLETTENBERG, Deutsche med. Wchnschr. **80**:376 (March 18) 1955.

Isoniazid was used in 182 cases of tuberculosis in a children's clinic. It is usually given in combination with other tuberculostatic drugs, mainly streptomycin. So far no case of tuberculous meningitis treated with this combination has relapsed. The same combination was given in cases of miliary tuberculosis and replaced after 30 days by paraaminosalicylic acid. Eight children 10-14 years of age had lung cavities. Here, in addition to the combined treatment, pneumothorax and operative measures are to be used. It seems that x-ray density of whole lobes with presence of tubercle bacilli in the fasting stomach juice has become more frequent since institution of the combined therapy. These densities clear up better without than with tuberculostatic therapy.

AMBERG, Rochester, Minn.

OXYTETRACYCLINE (TERRAMYCIN) IN THE TREATMENT OF OSTEOMYELITIS. F. WEBER, Med. Klin. **50**:669 (April 15) 1955.

Acute cases of osteomyelitis in 23 children 6-14 years of age were treated with oxytetracycline (Terramycin) administered intravenously and by mouth. Of the 23 cases, 11 were admitted between the second and fourth days of the disease. Treatment was started immediately, without waiting for identification of the causative organism or for determination of their resistance. All of these 11 cases recovered without complication. In addition to the oxytetracycline treatment, the diseased extremities were placed at absolute rest, and blood transfusions were given to the more severely ill. Twelve cases were admitted between the 7th and 10th days of the disease, when all had a subperiosteal abscess. The acute symptoms were also controlled with oxytetracycline, given as above, but also used locally on surgery. In only two cases oxytetracycline had to be stopped on account of diarrhea.

AMBERG, Rochester, Minn.

PRENATAL DISEASES ILLUSTRATED BY FOUR EXAMPLES. O. THALHAMMER, Wien. klin. Wchnschr. **67**:68 (Jan. 28) 1955.

Four cases are given to illustrate the influence of hunger, possible vitamin B_2 deficiency, quinine, and toxoplasmosis acting on the mother in early stages of pregnancy and on the children.

AMBERG, Rochester, Minn.

Acute Infectious Diseases

THE EPIDEMIOLOGY OF POLIOMYELITIS: A STUDY OF AN OUTBREAK IN PAYSON, UTAH, 1951. PAUL F. WEHRLE, California Med. **82**:314 (April) 1955.

In an unusually intense and severe outbreak of poliomyelitis, close personal contact, either directly or through intermediaries, with persons with poliomyelitis appeared to be the only significant factor common to the majority of the cases studied.

PRYOR, Redwood City, Calif.

TREATMENT OF FAVISM WITH CORTISONE. ARNOLD H. BECKER, J. A. M. A. **155**:1158 (July 24) 1954.

In a case of favism in a 2-year-old boy, the eighth case to be reported in the American literature, the use of cortisone proved to be an effective therapeutic measure.

KIMBALL, Evanston, Ill.

CURARE "HIBERNATION" AND ARTIFICIAL RESPIRATION OVER SEVERAL WEEKS IN THE TREATMENT OF A SEVERE TETANUS. E. ROSSI, A. BODMER, M. BETTEX, A. BUHLMANN, P. LUSHSINGER and K. GRAF, Schweiz. med. Wchnschr. **84**:1329 (Nov. 27) 1954.

The patient, a 13-year-old girl, started with symptoms of tetanus six days following a trauma. Curare was given to reduce stiffness and cramps. Gangioplegica (a mixture of Dolosal, Largactil and Phenergan) served as aid to "hibernation" on two days, together with cold, to abate a fever of about 40 to 38 C (104 to 100.4 F), aside from the sedative effect. Prolonged artificial respiration with tracheotomy was given, and tetanus antiserum, Pantopon, antibiotics, vitamins, and blood and plasma transfusions were given, and nutrition was maintained by gavage. The patient recovered.

AMBERG, Rochester, Minn.

RECENT THOUGHTS REGARDING RHEUMATIC DISEASE. F. DE MATTEIS, Minerva pediat. **6**:845 (Nov. 15) 1954.

In rheumatic fever, a disproteinemic state exists with colloid lability and both a tendency for intravascular aggregation and an increased viscosity of the red blood cells. Heparin is of therapeutic value in rheumatic fever by reason of a dispersive, antiexudative, and anticoagulative action, as well as its giving effects similar to that given by corticotropin (ACTH).

HIGGINS, Boston.

IMPORTANCE OF THE RAPID IDENTIFICATION OF THE VIRUS OF INFLUENZA. A. CURBELO and V. MARQUEZ, Arch. med. inf. **23**:337 (Oct.-Dec.) 1954.

The authors describe in a simple, brief, and clear form the means of rapid and sure identification of the virus of influenza. They feel that this may be achieved by any medical laboratory clinician, who need not be a specialist in virology. They also stress the importance which this type of diagnosis has for public health.

FROM THE AUTHORS' SUMMARY.

CAT-SCRATCH DISEASE WITH FATAL OUTCOME. SIEGFRIED GRAEFF, Monatsschr. Kinderh. **102**:232-237 (April) 1954.

The author reported the case of a 2½-year-old boy with cat-scratch disease which terminated fatally. No evidence or history of actual scratching by the cat was obtained, but it was ascertained that the patient lived in intimate contact with the animal (frequent kissing, etc.).

Significant autopsy findings were those of an acute infection with a primary complex in Waldeyer's pharyngeal ring and regional lymph node involvement.

The term "felinosis" was proposed as a better term than cat-scratch disease, as actual scratching by the cat is not necessary for the transmission of the disease.

HARTENSTEIN, Syracuse, N. Y.

SEGMENTAL X-RAY EXAMINATION OF THE CHEST IN PERTUSSIS. R. SEYSS, Monatsschr. Kinderh. **102**:243-244 (April) 1954.

By means of segmental chest x-rays, several patients with pertussis were found to have middle-lobe bronchus obstruction with complete triangular atelectasis distal to the obstruction. Although the obstruction itself was reversible, the atelectatic areas were found to remain present in a few cases.

HARTENSTEIN, Syracuse, N. Y.

CHOLANGITIS DUE TO LAMBLIA INTESTINALIS IN CHILDHOOD. HEINZ SPIESS, Monatsschr. Kinderh. **102**:417-419 (Sept.) 1954.

An 11-year-old boy seriously ill with high fever, pallor, mild icterus, light-colored stools, abdominal tenderness, and prolonged slight hepatomegaly was found to have Lamblia intestinalis in his duodenal and gall bladder contents. This was ascertained by duodenal intubation and examination of duodenal juices before and after intramuscular administration of hypophysin, the latter producing emptying of cholecystic contents into the duodenum. A diagnosis of cholangitis due to L. intestinalis was entertained, the patient was treated with quinacrine (Atabrine), and complete rapid clinical and parsitological recovery took place.

The author advocated examination of duodenal juices for L. intestinalis in all patients with obscure gastrointestinal illnesses who exhibit vague upper-quadrant abdominal pain, tenderness on palpation in the region of liver and gall bladder, and prolonged hepatic enlargement.

HARTENSTEIN, Syracuse, N. Y.

Diseases of Blood, Heart and Blood Vessels, and Spleen

RUPTURE OF THE SPLEEN. HERBERT F. PHILLIPSBORN Jr., HOWARD S. TRAISMAN, and DAVID GREER JR., New England J. Med. **252**:159 (Feb. 3) 1955.

Four cases of erythroblastosis fetalis with rupture of the spleen are reported. In one case the rupture, with hemorrhage into the phrenicolienal ligament, occurred before therapy. In the others replacement transfusion was carried out. All infants died.

Rupture of the spleen does occur in untreated erythroblastotic infants. There is no conclusive evidence that exsanguination transfusion contributes to rupture in infants affected with erythroblastosis fetalis.

Several factors which contribute to splenic rupture in erythroblastosis are enumerated. The authors believe that extramedullary hematopoiesis, increased phagocytosis, and tendency to hemorrhage are the factors most concerned.

WHEELOCK, Washington, D. C.

A STUDY OF THE CLINICAL REACTIONS TO VENOUS ANGIOCARDIOGRAPHY. FREDERIC L. ELDRIDGE, HERBERT N. HULTGREN, CHI KONG LIU, and MARGARET BLUMENFELD, New England J. Med. **252**:259 (Feb. 17) 1955.

Reactions to the rapid intravenous injection of iodopyracet (Diodrast), sodium iodomethamate (Neo-Iopax), and sodium acetrizoate (Urokon) are reported in 120 cases in which diagnostic venous angiocardiography was performed.

Severe reactions were more frequent after the use of iodopyracet and sodium iodomethamate than after that of sodium acetrizoate. Severe reactions appeared more frequently with larger doses, in younger patients, and in patients with cyanosis due to right-to-left intracardiac shunts. Of these three factors, the size of the dose appeared most important.

Multiple injections of contrast medium appeared to cause severer reactions than a single injection.

Six deaths occurred among 300 patients, a mortality of 2.%

Deaths occurred after the administration of all three contrast agents. Three followed the use of sodium acetrizoate. Five of the six patients who died were in poor clinical condition. Four

had severe congenital cardiac malformations; one patient with metastatic carcinoma had an obstruction of the superior vena cava, and one child had idiopathic cardiac hypertrophy with congestive heart failure.

FROM THE AUTHORS' SUMMARY.

THREE CASES OF AGAMMAGLOBULINEMIA. A CLINICAL, GENETIC AND PHYSICOCHEMICAL CONTRIBUTION TO THE KNOWLEDGE OF THE PROTEIN METABOLISM. N. KULNEFF, K. O. PEDERSEN, and J. WALDENSTROM, Schweiz. med. Wchnschr. **85**:363 (April 16) 1955.

Three cases of agammaglobulinemia are reported. The exact ages are not given, but they seem to be about 10, 7, and 6 years. The two older boys were brothers, the third was possibly related. His parents were first cousins. Paper electrophoretic determinations of the serum proteins were made, and in the case of the two brothers, free electrophoresis according to Tiselius was also carried out. The serum of all three was also studied by means of the ultracentrifuge. The boys had multiple infections. A complete lack of gamma globulin was found associated with a lack of the 7S component by ultracentrifuge. In contrast to acquired forms of agammaglobulinemia, the congenital form is looked upon as a chemical malformation (inherent error of metabolism) with loss of synthesis of gammaglobulin and the 7S component of serum protein. The literature is discussed. For further detail the paper is to be consulted.

AMBERG, Rochester, Minn.

POSTNATAL FORMATION OF FETAL HEMOGLOBIN. IRMGARD GREINACHER, Monatsschr. Kinderh **102**:522-524 (Dec.) 1954.

In two newborn infants with erythroblastosis fetalis due to Rh incompatibility who had received exchange transfusions within 24 hours after birth, fetal hemoglobin dropped to below 5% shortly after the procedure. However, after a few days it rose to 18% and 10.5%, respectively.

HARTENSTEIN, Syracuse, N. Y.

PREVENTION OF TRANSFUSION ACCIDENTS WITH VITAMIN P (RUTIN). H. EWERBECK and R. LEGERSKI, Monatsschr. Kinderh. **103**:21-23 (Jan.) 1955.

Twenty rabbits were sensitized against human erythrocytes and against human whole blood. Shocking doses of these antigens were administered 9-11 days later.

Intravenous administration of vitamin P (rutin) in the dose of 90 mg. either together with the sensitizing injection of the antigen or with the shocking dose did not prevent anaphylactic shock or decrease its severity.

Use of vitamin P in the prophylaxis of transfusion accidents in humans could, therefore, not be recommended at the present time.

HARTENSTEIN, Syracuse, N. Y.

EARLY AND LATE RESULTS AFTER EXCHANGE TRANSFUSIONS OF CHILDREN WITH ICTERUS GRAVIS. H. KÖLBL, Wien. klin. Wchnschr. **67**:172 (March 11) 1955.

Of 112 infants with icterus gravis which were treated early with exchange transfusions, 104 developed normally. Due to a tear of the tentorium during birth, four infants died; one died after exchange transfusion with Rh+ blood, and one died in the seventh week with plasmacellular pneumonia. Twenty newborn infants received the exchange transfusion late, that is, from the 3d to the 11th day of life. Of these, only 2 infants developed normally; in 12, signs of cerebral damage developed. Six of the 20 cases died; 4 with liver injury and kernicterus, 1 as a result of birth trauma, and 1 had received Rh+ blood. Even poorer results were obtained when the infants received only transfusions with Rh— blood. Infections, mainly of the skin, could be prevented by the use of antibiotics at the time of the exchange transfusions. A pseudoaplastic anemia which occurs usually on the 10th to 19th day, also after exchange transfusion, could be avoided by administration of 2.5 mg. corticotropin (ACTH) the first 3 days. The follow-up extended over a period of six months to seven years. The cerebral manifestations are discussed as well as lasting liver injuries. Hyperallergic dermatoses were seen in 82 of the normally developing children. The frequency of enamel hypoplasia and enamel defects is pointed out, and the yellowish greenish discoloration of the first teeth is referred to as biliverdin. Early caries is common with signs of osteoporosis and disorders of calcification on x-ray examination. The chemical analysis for fluorine in enamel and dentin of the teeth showed a marked diminution compared with that of normal teeth.

AMBERG, Rochester, Minn.

Diseases of Nose, Throat, and Ear

DIFFERENTIAL DIAGNOSIS AND MANAGEMENT OF COUGH. JOSEPH J. FURLONG, California Med. **81**:297 (Nov.) 1954.

Cough is a complex defensive reflex whose purpose is protection of the respiratory tract. There are many nonrespiratory causes, particularly pulmonary congestion from heart disease. Coughs may be useful, useless, or harmful. Treatment based on etiology and type of cough requires only a few medications whose efficiency has been demonstrated.

The meaning of cough as a symptom must be carefully determined before rational treatment can be planned. Recent researches on the physiology of the cough reflex, the bronchi, and the mechanisms of bronchial secretion have made it possible for a physician to plan a treatment program on a firm scientific basis, rather than on tradition.

PRYOR, Redwood City, Calif.

CORRECTION OF CONGENITAL ANOMALIES OF THE EAR. EUGENE L. DERLACKI and GEORGE E. SHAMBAUGH JR., Illinois M. J. **105**:107-109 (March) 1954.

Since the particular anomaly in each case varies considerably and no one technique can be suitable for all cases, the authors of this article believe that in each case the surgical procedure should be fitted to the condition that is found, keeping in mind that the aim is to construct a sound conductive system that will most nearly approach the normal impedance-matching mechanism. There is a marked tendency for anomalies of the inner ear to be independent of anomalies of the outer and middle ear. Of the 24 operations completed for improvement of the hearing in this study by the authors, all received an initial hearing gain. In three the gain was not maintained. Of the 21 ears with maintained improvement in hearing, 13 are at the practical 30 db. level or better at the most recent test.

BARBOUR, Peoria, Ill.

DIAGNOSIS AND TREATMENT OF SECRETORY OTITIS MEDIA. PIERCE W. THEOBALD, Illinois M. J. **105**:313-317 (June) 1954.

Secretory otitis media is being encountered more frequently and being diagnosed more frequently than previously. Etiology of the disease is blockage of the Eustachian tubes due to infection, allergy, or mechanical factors. Secretory otitis media may cause a considerable hearing loss, but if proper treatment is instituted the loss is a reversible one.

The diagnosis is made from the history, the appearance of the tympanic membrane, inflation and auscultation of the middle ear, and diagnostic myringotomy if necessary. Although conservative therapy may often be of value in children, it rarely is so in adults. Secretory otitis media in children is usually an indication for tonsillectomy and adenoidectomy.

Prognostication is difficult, for often there is no relationship between duration of symptoms and time required to effect a cure.

FROM THE AUTHOR'S SUMMARY.

THE RELATIONSHIP OF AUDITORY DISCRIMINATION TO ARTICULATORY DEFECTS OF CHILDREN WITH NO KNOWN ORGANIC IMPAIRMENT. ERNEST KRONVALL and CHARLES DIEHL, J. Speech & Hearing Disorders **19**:335-338 (Sept.) 1954.

Thirty elementary-grade children diagnosed as severe functional articulatory defectives were matched on the basis of chronological age, sex, grade, and intelligence with 30 normals. The elementary-grade children with severe functional articulatory disorders exhibited significantly more errors in speech-sound discrimination on the Templin Speech Sound Discrimination Test.

PALMER, Wichita, Kan.

DIFFICULTIES IN SWALLOWING IN CHILDREN. P. MOUNIER-KUHN and A. PERSILLON, Pédiatrie **10**:37, 1955.

This very thorough review of the subject, illustrated by 15 x-ray reproductions and numerous case reports and documented by three pages of references of the world literature, is divided into three parts.

The first part presents briefly the anatomical and physiological conditions necessary for the act of swallowing. The second part discusses swallowing disturbances in the infant. Physiologically, each infant must develop the reflexes and coordination of the various phases of swallowing, and this period of learning may be delayed, as demonstrated by the case of a

premature girl 12 to 15 days of age who at first was believed to have tracheoesophageal fistula. The true disturbances in this age group are divided into those caused by malformations and anomalies of the gastrointestinal tract as well as the central nervous system, infections or tumors affecting the process of swallowing directly or indirectly, nervous disturbances, such as anorexia nervosa, spasms of the esophagus, meningeal hemorrhages, or the effect of drugs, and accidental disturbances, such as foreign bodies.

The third part presents swallowing difficulties in the older child, such as those produced by infections causing paralysis of the palatopharyngeal muscles due to diphtheria, or those on a nervous basis (poliomyelitis, Guillain-Barré's syndrome, dermatomyositis, tumors affecting the brain stem, and encephalopathies. An important group includes pathological changes of the esophagus itself, such as stenosis of the esophagus of delayed appearance, compression from without, spasms, megaesophagus, varicose veins, diphtheria of the esophagus, thrush, peptic ulcer, stenosis as a result of corrosive burns, and foreign bodies. GLASER, Baltimore.

THE PROBLEM OF TONSILS. R. POCH VINALS, Arch. pediat. Barcelona **4**:439-466 (Jan.-Feb.) 1954.

The author reviews the problem of tonsil and Waldeyer ring infections and comes up with the following conclusions.

1. The tonsils and the entire group of adenoidal tissue composing Waldeyer's ring have a function in antibody formation.

2. This is a double function in which the tonsils assist the phagocytic and reticuloendothelial system on the one hand and the lymphocytes on the other.

3. So-called hematogenous infections of Waldeyer's ring are completely understandable as a fixing agent rather than an eliminating system for infections. In spite of the frequency with which tonsils are affected in hematogenous infection, these infections arise from the outside, not within the tonsillar tissue.

4. The cryptic nature of the tissue gives a favorable place for antibody formation.

5. The formation of antibodies to combat agranulocytic infections is a normal part of the tonsil function.

6. It appears that eventually tonsillar tissue will be found to have a function in the elaboration of proteins. Globulins are found around lymphoid follicles. The globulins are certainly abundant in tonsillar lymphosarcomas. The equilibrium between infection and immunity gives rise at times to the production of true centrofollicular granulomas.

7. The endothelial capillary inflammation explains in large part the symptoms associated with tonsillitis.

ALLEN, Santa Fe, N. Mex.

Diseases of Lungs, Pleura, and Mediastinum

SPONTANEOUS MEDIASTINAL EMPHYSEMA IN ON INFANT. G. CONCA, Pediatria **62**:602 (July) 1954.

In a 3-month-old infant, mediastinal emphysema (Hamman's syndrome) developed during the course of bronchopneumonia. From autopsy findings, a polycystic degeneration of the middle lobe of the right lung appeared to be the underlying cause of the mediastinal emphysema.

HIGGINS, Boston.

STAPHYLOCOCCUS PNEUMONIA IN CHILDREN. G. BARDOSOVA and J. KUCERA, Pediat. listy **9**:258, 1954.

A clinical report on 66 pneumonia cases caused by Staphylococcus is presented. Twenty of them were complicated by empyema.

FROM THE AUTHORS' SUMMARY.

RHEUMATIC PNEUMONIA. I. BOR and H. PADOVCOVA, Pediat. listy **9**:265, 1954.

From 681 patients suffering from acute rheumatism who were observed for a period of seven and one-half years in Second Children's Hospital, 42 were selected who showed clinically or by section a lung disease.

In nine cases rheumatic pneumonia was proved by a section or histological test. In 20 further cases the diagnosis was made on basis of clinical development and symptoms of the mentioned illness; these were typical in each of the 29 cases. The children's ages were from 2 to 16 years.

The clinical view and laboratory results are described.

Treatment by corticotropin (ACTH) or cortisone is recommended with high doses of antibiotics as well as strophanthin and oxygen at the same time.

FROM THE AUTHORS' SUMMARY.

ACQUIRED CAVITIES IN THE LUNG. EMMA J. MEYERS, Maandschr. kindergeneesk. **22**:54-56 (Feb.) 1954.

The author draws attention to the formation of cavities in the lung which frequently are under pressure. These cavities arise during pyogenic infections. They have a tendency to heal more quickly than abscesses. On the x-ray picture there is no fluid level.

A case is described of multiple lung abscesses during osteomyelitis which were followed roentgenologically and seen to regress with annular shadows. VAN CREVELD, Amsterdam.

THE CONSTITUTIONAL SIGNS OF ASTHMA IN CHILDHOOD. G. J. HUËT, Maandschr. kindergeneesk. **22**:73 (March) 1954.

The author describes an investigation on 187 asthmatic children from an asthma clinic. The pulmonary function was established in 66 of these children. There seemed to be a close correlation between the severity of the asthma and the pattern of the pulmonary function. There was an improvement of pulmonary function with age. Comparable values for normal children are not given. It further appeared that a positive family history, eczema, and other skin lesions were more frequent in the children with severe asthma than in children with mild asthma. The average age of the beginning of the attacks was in the severe group 2 years and 10 months and in the mild group 4 years and 3 months. These observations support the view of the author that two forms of asthma can be distinguished. VAN CREVELD, Amsterdam.

BRONCHOGRAPHY WITH MIXTURES OF IODIZED OIL AND SULFADIAZINE. J. N. BOET, Nederl. tijdschr. geneesk. **98**:78-80, 1954.

Iodized oil (Lipiodol) has the disadvantage that it may remain for a long time in the alveoli. Radiological check-ups are made difficult in this way. Watery suspensions were too irirtating. A more viscous fluid of mixtures of iodized oil and sulfadiazine has been proved useful. Within four hours most of the contrast medium has been expectorated. Forty-eight hours later the lungs are clear. Peripheral branches of the bronchial tree, however, do not fill adequately. In purulent bronchitis with bronchiectasis, pure iodized oil is preferred as this fills the small branches better. Twenty milliliters of iodized oil was mixed with 3 gm. of sulfadiazine. It is advisable to commence a bronchographic investigation with this mixture. If no adequate filling of the smaller bronchi is seen, another bronchogram should be made with ordinary iodized oil. VAN CREVELD, Amsterdam.

Diseases of Gastrointestinal Tract, Liver, and Peritoneum

CONGENITAL DIAPHRAGMATIC HERNIA. BURTON E. ADAMS, California Med. **81**:332 (Nov.) 1954.

Treatment of congenital diaphragmatic hernia in infants is a matter of semiemergency and should be done as soon as adequate preparations can be made because sometimes fatal complications develop swiftly. In preoperative preparation there is great advantage in thorough decompression of the abdominal viscera, stomach, bowel, and bladder. As to operation, the author believes the abdominal approach has most to recommend it. In the postoperative period, continued gastric suction for a brief time, parenteral administration of fluids, and use of a Mistogen tent with a high moist oxygen content will facilitate rapid recovery.

PRYOR, Redwood City, Calif.

A Case of Phaeochromocytoma in Childhood. M. Israelski, A. C. Kendall, and R. E. Shaw, Arch. Dis. Childhood **29**:18 (Feb.) 1954.

A case of pheochromocytoma in a boy aged 10 years is described. The piperoxan (benzodioxan) test was positive, and the urinary excretion of norepinephrine was markedly raised. Retroperitoneal pneumography demonstrated the tumor, which was successfully removed.

Kelly, Milwaukee.

Laboratory Observations on the Viscidity of Meconium. John L. Emery, Arch. Dis. Childhood **29**:34 (Feb.) 1954.

A series of 64 specimens of normal meconium were examined for "surface tension," water content, nitrogen, and tryptic activity. Extremely wide ranges were found in all factors. The viscidity of the meconium is directly related to the water content. It appears to be inversely related to the nitrogen content, and unrelated to the tryptic activity of meconium. Specimens from four cases of meconium obstruction showed a greatly diminished water content, normal nitrogen, and normal or low tryptic activity.

Kelly, Milwaukee.

Benign Giant Tumor of the Abdomen in a One and One-Half Year Old Child. G. Zbinden, Ann. Paediat. **183**:240 (Oct.) 1954.

The author describes multilocular cystoma of the biliary duct in a girl of 1 7/12 years old which weighed nearly 3 kg. It had led to an ileus and was successfully operated on. The benign tumor originated probably from aberrant biliary ducts of the right hepatic lobe.

From the Author's Summary.

Enteritis Regionalis in Infancy. R. Uebelhart, Schweiz. med. Wchnschr. **84**:1336 (Nov. 27) 1954.

An infant about 3 months of age was operated on for an umbilical hernia. About a month after surgery abdominal symptoms developed. Some parts of the small intestines were found on operation to be closely adherent, and a stretch of about 12 cm. of the lower ileum presented a number of perforations; leaving the last 11 cm. free and appearing normal. The author calls this a regional enteritis with reference to a traumatic origin. The patient died, and the postmortem findings are given.

Amberg, Rochester, Minn.

Cystic Fibrosis of the Pancreas in an Infant. P. Nicolaj, Clin. pediat. **36**:669 (Sept.) 1954.

An 8-month-old infant had the typical symptoms and clinical course of cystic fibrosis of the pancreas. The glucose tolerance test showed a striking fall in the blood sugar content to 0.045% one and one-half hours following the ingestion of the sugar. The test for tryptic potency in the feces on a photographic film showed no digestion of the gelatin.

Higgins, Boston.

The Diaphragmatic Hernia of Morgagni in Children. B. Carletti and L. Papagni, Minerva pediat. **6**:840 (Nov. 15) 1954.

An infant 6 months of age was found to have a diaphragmatic hernia, through which a portion of the transverse colon had entered the thoracic cavity through the foramen of Morgagni (Larrey's window). This triangular opening is at the attachment of the diaphragm to the lower sternum. The diagnosis was readily established by x-ray examination with the child in the lateral position and following a barium enema. This type accounts for about 1½% of diaphragmatic hernias. The patient's symptoms included dyspnea, cyanosis, cough, colic, vomiting, hematemesis, and anemia.

Higgins, Boston.

Congenital Duodenal Occlusion. B. Possenti and A. Gianelli, Minerva pediat. **6**:874 (Nov. 15) 1954.

Four cases are reported of duodenal occlusion in newborn infants. The causes of the obstructions were (1) an intrinsic narrowing (ring-like) of the duodenum above the ampulla

of Vater, (2 and 3) extrinsic adhesions probably due to fetal peritonitis, and (4) pressure of the annular pancreas. Surgery was resorted to with each of the infants, but three of them died within a few hours because of their extremely poor preoperative physical condition; the fourth child died two months later from recurrence of the adhesions.

HIGGINS, Boston.

THE BLOOD PICTURE IN INFANTS AND CHILDREN WITH GASTROINTESTINAL DISTURBANCES, AND ITS RELATION TO THE FUNCTION OF THE ADRENAL CORTEX. C. GAMBARO, Pediatria **62**:578 (July) 1954.

The differential blood cell count and Arneth's classification are practically identical in infantile diarrhea and in Addison's disease. Thus it seems likely that adrenal deficiency may be the cause of many of the symptoms of infantile diarrhea.

HIGGINS, Boston.

EMERGENCY SURGERY OF DIGESTIVE TRACT IN THE NEWBORN. B. TARACENA DEL PINAL, L. GONZALEZ CORVIELLA, and J. DONADEN, Acta pediat. españ. **12**:1050-1061 (Nov.) 1954.

The authors discuss their experiences with gastrointestinal surgery of the newborn at the Infants Pavilion Hospital of the Red Cross, in Madrid. The article is in three parts: (1) the need of early and correct diagnosis; (2) preoperative treatment, and (3) social aspects of the problem.

The types of surgery discussed are esophageal lesions, gastric and intestinal defects, and biliary anomalies. They emphasize the need for medical and surgical centers for surgery of this type and the necessity of getting this knowledge to general practitioners so that they may lose fear of surgical intervention in the newborn.

ALLEN, Santa Fe, N. Mex.

INTESTINAL OCCLUSION DUE TO MECONIUM IN THE NEWBORN. R. BORCELLS POR, Rev. españ. pediat. **10**:595-606 (Sept.-Oct.) 1954.

The author reviews the literature and describes the pathology, symptoms, and x-ray findings in intestinal occlusion due to meconium. He regards it as a complication of a primary pancreatic insufficiency—fibrosystic disease of the pancreas. Not all cases of pancreatic insufficiency develop this symptom.

Treatment, medical and surgical, is described. Surgery should not be attempted unless there is reasonable expectation of a good result. The two surgical methods, (1) enterostomy and intestinal lavage and (2) Mikulicz operation and double ileostomy, are described in detail. The advantages and disadvantages of each type procedure are explained. Postoperative care is also described.

ALLEN, Santa Fe, N. Mex.

CONGENITAL OCCLUSION DUE TO INTESTINAL INFARCT. JUAN PECANOL, Rev. españ. pediat. **10**:639 (Sept.-Oct.) 1954.

The author gives a case history of a 7-day-old infant diagnosed as congenital obstruction. Surgical intervention showed a gangrenous area with thrombosis in the mesenteric artery and typical infarct formation. Surgical removal was successful, and the child lived seven days after the operation. Necropsy showed many other vascular lesions and histologically proved the cause to be an infarction.

Several cuts showing pathology and histology of the lesions as well as a preoperative x-ray with barium meal are included.

ALLEN, Santa Fe, N. Mex.

EPIDEMIC VOMITING. G. A. VON HARNACK, Deutsche med. Wchnschr. **80**:639 (April 22) 1955.

An institutional epidemic is reported which attacked 21 of 46 children 3 to 14 years of age and 2 of 7 adults. Violent vomiting was the main feature, associated with strong nausea. The vomiting may come very suddenly in the night and can be projectile. Vomiting may occur only once or twice. Abdominal pain, occasionally headaches, vertigo, and diarrhea may be present. Low fever was rarely missed. Complete recovery takes place in one to two and one-half days. The incubation period is usually two days (one and one-half to seven days). Bacteriological examination as well as search for virus were not successful, but by means of ultrafiltrates transfer to volunteers was possible.

AMBERG, Rochester, Minn.

THE PROBLEM OF THE TREATMENT OF DILATATION OF THE LARGE INTESTINE: HIRSCHSPRUNG'S DISEASE AND IDIOPATHIC MEGACOLON. T. NAEGELI and H. J. BETZLER, Med. Klin. **50**:558 (April 8) 1955.

The idiopathic megacolon is said to differ from Hirschsprung's disease in that the dilatation begins immediately adjoining the anus. Of the 10 cases observed, two were seen in boys 5 and 7 years of age. A detailed history is given. Treatment with the sympathicolytic dihydroergotamine was not successful. The resection of the dilated part of the large intestine is indicated.

AMBERG, Rochester, Minn.

CONGENITAL PYLORIC STENOSIS AS A FACTOR PREDISPOSING TO THE ULCER SYNDROME. O. STEINICKE NIELSEN, Acta pædiat. **43**:432 (Sept.) 1954.

In order to study whether peptic ulcer and gastritis occur more frequently in individuals with previous congenital pyloric stenosis than in others, the author has questioned 95 individuals (73 men and 22 women) between the ages of 25 and 45, who had all in early infancy been treated medically for congenital pyloric stenosis in a children's hospital. Information was thus obtained on the present and previous states of health of the individuals, especially on possible dyspeptic complaints. Similarly a control group of 100 nonselected hospitalized patients (77 men and 23 women) between the ages of 25 and 51 years were questioned. In the starting series it was found that 28% had gastritis or peptic ulcers against 12% in the control group.

Adults with previous congenital pyloric stenosis thus presented a higher incidence of gastritis and peptic ulcer than the control group. In addition, the investigation revealed a considerably higher incidence of gastritis and peptic ulcer among the parents and siblings of the questioned subjects in the starting series than among the corresponding relatives in the control group.

FROM THE AUTHOR'S SUMMARY.

SPONTANEOUS PNEUMOPERITONEUM. J. J. PIETERSE and J. SLOOFF, Maandschr. kindergeneesk. **22**:96 (March) 1954.

Two patients with "spontaneous" pneumoperitoneum are described. The first child was admitted to hospital two days after a normal birth at term, because of vomiting and meteorism. X-ray examination revealed a pneumoperitoneum, localized mainly under the diaphragm. The surgeon considered exploration of the abdomen too great a risk. By means of puncture, 180 ml. of air escaped. The child improved after the puncture, and there was a complete recovery.

The second child was a 17-day-old Mongoloid premature infant with a birth weight of 1980 gm. It was admitted to hospital because of nuclear jaundice, caused by a A-O blood-group antagonism and was treated with corticotropin (ACTH). Three days later symptoms of pneumonia appeared, and still two days later the abdomen was distended. X-ray examination revealed pneumoperitoneum. After puncture the child recovered. Three months later the child died from pneumonia. At autopsy no abnormalities were found in the abdomen; there was, however, a small diverticulum of the ileum, but no signs of a preceding perforation.

VAN CREVELD, Amsterdam.

A CASE OF MECKEL'S DIVERTICULUM IN THE EPIGASTRIUM. A. M. VAN HERK, Nederl. tijdschr. geneesk. **22**:2431 (Aug. 28) 1954.

A Meckel's diverticulum gives rise to clinical signs in the hypochondrium. A patient is described who complained of acute violent pains in the epigastrium, while the lower regions of the abdomen remained normal. The tentative diagnosis was a penetrating or perforating ulcer of the stomach. Laparotomy revealed a diverticulum with several pouches in the epigastrium. Heterotopic tissue could not be demonstrated. The patient's convalescence after the operation was uninterrupted.

VAN CREVELD, Amsterdam.

LOWERING OF ALBUMIN AND FRACTIONS OF THE GLOBULIN, AND INCREASE OF GAMMA GLOBULIN, A NEW SIGN OF COMA HEPATICUM. C. K. V. VAN DOMMELEN and M. J. SCHULTE, Nederl. tijdschr. geneesk. **22**:2878-2880 (Oct. 9) 1954.

Paper electrophoresis of the serum from three patients suffering from serious hepatic insufficiency caused by hepatitis revealed some characteristics. The albumin content was

decreased and the gamma globulin fraction increased, as often is described in literature. In addition to this the beta- and alpha-2 globulin content were decreased to abnormally low levels. These last results are very characteristic and have a bad prognostic significance. One of the three patients recovered from this serious illness.

VAN CREVELD, Amsterdam.

Nervous Diseases

MENINGEOMA IN THE REGION OF THE PINEAL GLAND IN CHILDREN. FRITZ HEPPNER, Wien. klin. Wchnschr. **67**:145 (Feb. 25) 1955.

Three cases of meningeoma of the tela choroidea ventriculi tertii in children are reported. Two were operated on successfully, a 14-year-old girl and an 8-year-old boy. The third case, that of a 4-month-old girl, was not seen by the author. The infant died after extirpation of the tumor. Attention is called to the great rarity of meningeomas in the roof of the third ventricle. The neurological picture is not specific. The main manifestation is a blocking of the aqueduct. On x-ray examination a similarity exists with pinealomas. The growth is slow, the nature benign, and the delineation good, justifying surgical intervention, which is more promising than in cases of blastoma of the pineal gland.

AMBERG, Rochester, Minn.

Diseases of Genitourinary Tract

URETERAL OBSTRUCTION IN CHILDREN. OLE J. JENSEN JR. and S. WILLIAM CONROY, Northwest Med. **53**:586 (June) 1954.

The authors report 22 cases of urinary tract obstructions in a children's hospital observed over a four-year period. They emphasize the importance of early diagnosis and treatment and deplore the delay entailed by the use of antibiotic therapy as a substitute for adequate urological examination.

DOCTER, Seattle.

SIMPLE OVARIAN CYST IN A NEWBORN INFANT. RICHARD C. SMITH, Pediatrics **14**:232 (Sept.) 1954.

A case of a simple serous cyst of the ovary in a newborn is presented. This is believed to be the fifth such case in the literature. A short review of the pertinent literature is given.

FROM THE AUTHOR'S SUMMARY

REPORT OF A CASE OF OSTEONEPHROPATHY WITH VASCULAR CALCIFICATION IN INFANCY. E. P. PENDERGRASS and F. P. BROOKS, Radiology **62**:227-233, 1954.

The development of calcification in the vessels was observed in an infant girl 12 months of age after four months of treatment in the hospital for renal rickets. The changes in the long bones consisted of broadening of the shafts, flaring of the ends of the diaphyses, bowing, prominence of trabeculae, and periostial proliferation. Old infractions of ends of radii and ulnae were present. Later a ground-glass type of osteoporosis of the long bones appeared, and the periphery of the epiphyseal centers showed increased density. The x-ray appearance suggested the presence of both scurvy and rickets. Granular mottling of the skull and healing fractures of the lower ribs were part of the roentgen picture. The patient died before reaching the age of 2 years.

This report includes a brief discussion of 14 other cases of "renal rickets" in which calcification of the vessels developed. All appeared to have a severe renal disease of inflammatory or congenital nature, and secondary parathyroid hyperplasia was a factor in the mechanism of the bony changes. Metastatic calcifications were seen in most patients.

ANSPACH, Riverside, Ill.

HORMONAL SEX REVERSAL IN A FEMALE. W. J. MATHESON and E. M. WARD, Arch. Dis. Childhood **29**:22 (Feb.) 1954.

A case is described of congenital adrenal hyperplasia in which there were male external and female internal genitalia. The gonads were ovaries. There was a prostate and posterior urethral valves causing urinary stasis.

It is suggested that virilization began at a much earlier stage of development than is usual in hormonal sex reversal but that the paramesonephric duct system developed normally because it is unresponsive to adrenal androgen.

KELLY, Milwaukee.

A CONGENITAL RENAL TUBULAR DEFECT. J. LUDER and DOROTHY BURNETT, Arch. Dis. Childhood **29**:44 (Feb.) 1954.

A case is presented of polyuria and polydipsia resistant to vasopressin injection (Pitressin) in a child of 9 months. The main symptoms are vomiting, irritability, failure to thrive, and intermittent fever associated with dehydration. The biochemical findings showed a tendency to hyperelectrolytemia, which could be controlled only with a very large fluid intake. The cause is considered to lie in a congenital defect of the renal tubules in which there is a failure of water reabsorption. Previous cases are mentioned, and suggestions are offered regarding the management and prognosis of these cases.

KELLY, Milwaukee.

INFECTIONS OF THE URINARY TRACT IN INFANCY AND CHILDHOOD. C. W. G. LEE, M. J. Australia **1**:634-635 (April 24) 1954.

Lee describes the difficulties in interpreting urinary findings and symptoms in infections of the urinary tract in infancy and childhood and the treatment of them.

The clinical course of 382 cases of pyuria is reviewed.

MCGUIGAN, Evanston, Ill.

FREQUENCY, PROGNOSIS AND TREATMENT OF THE NEPHROSIS SYNDROME. J. FRIDERICH, A. PRADER, and G. FANCONI, Helvet. paediat. acta **9**:109 (June) 1954.

Graphic representation is given of results of treatment with corticotropin (ACTH) (50 cases) and Thiosemicarbazone (12 cases) and of frequency and prognosis of nephrosis.

FROM THE AUTHORS' SUMMARY.

NEPHROSIS AND BODY GROWTH. H. BAUER, Helvet. paediat. acta **9**:127 (June) 1954.

The rate of growth was studied in 34 cases of nephrotic syndrome. Before onset of the disease the rate was normal; during the disease the rate was progressively slowed. After termination of the disease, a period of time approximately double that of the illness was necessary before the children attained their expected places on the anthropometric charts of the Children's Medical Center of Boston. The retarded rate of growth is probably caused by hypoproteinemia or the underlying disturbance of the protein metabolism.

FROM THE AUTHOR'S SUMMARY.

A CASE OF IDIOPATHIC HYPOALBUMINURIA WITH AMINOACIDURIA IN AN INFANT. J. DVORAK, A. KUBOVY, Z. ZAZVORKA, and J. HONS, Helvet. paediat. acta **9**:258 (July) 1954.

A history is given of an infant who was edematous at birth and who was clinically observed from 2 to 5 months of age. There occurred a hypoproteinemia and a hypoalbuminemia but no proteinuria. The amino acids are constantly increased in the serum and urine. Actually there is an insufficient production of plasma proteins, probably as a result of a functional disturbance of the liver or of the reticuloendothelial system. After treatment with vitamin B_{12} and transfusions the disturbances ceased.

FROM THE AUTHORS' SUMMARY.

EEG FINDINGS IN ENURESIS. YRJÖ TEMMES and ERKKI TOIVAKKA, Acta pædiat. **43**:259 (May) 1954.

Fifty-four cases of children with enuresis as cardinal clinical signs were examined with the aid of EEG. Thirteen of them had previously suffered from convulsions. In about 70% there were nontypical paroxysmal dysrhythmias or epileptic potentials. Only 11 cases had no changes in the EEG. It would seem that disturbances of cerebral origin in the control and communication of the bladder must be assigned a more important etiological significance than many a disorder or conflict of personality.

FROM THE AUTHORS' SUMMARY.

Diseases of Ductless Glands; Endocrinology

FLUOROHYDROCORTISONE AND CHLOROHYDROCORTISONE, HIGHLY POTENT DERIVATIVES OF COMPOUND F. ALAN GOLDFIEN, JOHN C. LAIDLAW, NAJIB ABU HAYDAR, ALBERT E. RENOLD, and GEORGE W. THORN, New England J. Med. **252**:415 (March 17) 1955.

Of interest to pediatricians is the fact that satisfactory inhibition of the adrenal cortex has been achieved with doses of 1 or 2 mg. of fluorohydrocortisone by mouth a day in normal subjects and in female patients with the adrenogenital syndrome. In male patients with a mixed clinical picture due to bilateral adrenal hyperplasia, adrenal inhibition was demonstrated at dosage levels of 5 and 25 mg. of fluorohydrocortisone daily. The chemistry of the potent substances is reviewed.

WHEELOCH, Washington, D.C.

BLOOD SUGAR LEVELS IN BABIES BORN OF DIABETIC MOTHERS. GEORGE M. KOMROWER, Arch. Dis. Childhood **29**:28 (Feb.) 1954.

Estimations of the blood sugar level during the first 24 hours of life were made on 21 normal infants and 40 infants born of diabetic mothers. Twenty-five of the latter 40 babies were given 50% glucose in the first eight hours of life.

The normal infants showed a wide scatter of blood sugar levels, but there was no dramatic rise or fall in the figures in any one case.

The babies of diabetic mothers revealed a rapid drop in the first hours of life, with a slow rise toward the end of the first 24 hours. There were considerable variations in the figures obtained.

The administration of a 50% oral glucose solution did not make any appreciable difference to the blood sugar levels obtained compared with the group of infants to whom glucose was denied.

KELLY, Milwaukee.

THE SIGNIFICANCE OF THE SODIUM ION FOR RETENTION OF CHLORIDE ON DESOXYCORTICOSTERONE ACETATE ADMINISTRATION. P. JEANNERET, A. F. ESSELLIER, and H. J. HOLTMEIER, Schweiz. med. Wchnschr. **85**:299 (March 26) 1955.

The influence of desoxycorticosterone acetate (DOCA) was studied on the urinary output of sodium and chloride ions in healthy individuals on low sodium but normal chloride intake. This is accomplished by the use of cation exchanges or by a low salt diet supplemented with ammonium chloride. DOCA did not influence directly the tubular mechanism for water and chloride reabsorption, and the chloride retention on DOCA administration with a normal sodium chloride intake is a secondary effect of the sodium retention. Only the sodium and not the chloride intake must be restricted in order to avoid the sodium-, chloride-, and water-retaining effects of adrenal cortex hormones in patients with normal adrenals subjected to cortical steroid treatment.

AMBERG, Rochester, Minn.

DISORDERS OF PUBERTY. G. FANCONI, Deutsche med. Wchnschr. **80**:337 (March 11) 1955.

Various features of normal puberty are discussed and their physiological variations in boys and girls. Hypothalamic pubertas praecox is contrasted with pseudopubertas praecox. This latter is conditioned not by the hypothalamic pituitary system but below this by disorders in the path between the hypothalamus and the gonads—there ovulation and spermatogenesis is absent. The adrenogenital syndrome is outlined. Attention is called to the transitory infantilism of pubertas tarda, as well as the true primary and the secondary hypogonadism. The true primary hypogonadism is due to lesion of the gonads, the secondary to disorder of the hypothalamic pituitary system. Obesity of puberty and emaciation of puberty and adolescence are outlined, and the psychic peculiarities of pubescence are considered. Under the various headings, therapeutic measures are given place.

AMBERG, Rochester, Minn.

Diseases of Muscles, Bones, Joints, and Lymph Nodes

RHEUMATOID ARTHRITIS (STILL'S DISEASE) IN CHILDREN TREATED WITH LONG COURSES OF ACTH AND CORTISONE. F. KUIPERS, Maandschr. kindergeneesk. **22**:109 (April) 1954.

The author gives a description of 12 children under 15 years of age treated with corticotropin (ACTH) or cortisone during 1 to 12 months (average, 3½ months). In eight patients

this treatment was combined with gold salts and amidopyrine when renewed signs of activity occurred during or after therapy. The treatment was combined with simple orthopedic measures and exercise therapy. The author states that it is important to treat patients with a low dosage of corticotropin (four times daily, 2 to 3 units) or cortisone (three times daily, 5 to 10 mg.). At the follow-up visit between 2 and 36 months (average, 14 months) after the cessation of all therapy, the function of the joints was noted to be much improved in the cases in which therapy had been started late in the course of the disease, and no joint deformity was seen in the cases in which therapy had been started early. Therapy with amidopyrine and gold salts is necessary to suppress renewed activity.

VAN CREVELD, Amsterdam.

Diseases of Eye

THE ASSOCIATION OF RETROLENTAL FIBROPLASIA WITH CEREBRAL DIPLEGIA. T. T. S. INGRAM and J. D. KERR, Arch. Dis. Childhood **29**:282 (Aug.) 1954.

Six cases have been described in which retrolental fibroplasia and cerebral diplegia occurred in association.

While both conditions are liable to occur in premature infants, it appeared probable that the frequency of the association was greater than was accounted for by chance and that in addition to prematurity other common etiological factors were operative.

Possible etiological factors have been discussed. These factors, which were frequently multiple, included abnormal pregnancy, abnormal delivery, and postnatal asphyxia.

Prolonged oxygen therapy had been given to each of the six cases under review, but whereas there is clinical and experimental evidence that oxygen therapy may be closely related to the incidence of retrolental fibroplasia, the same does not apply to cerebral diplegia.

It is suggested that anoxia in the prenatal and postnatal periods, resulting from the abnormalities described, is important in determining the association of retrolental fibroplasia and cerebral diplegia in a proportion of prematurely born infants.

KELLY, Milwaukee.

INFLUENCE OF VARIOUS CLIMATES UPON MORTALITY AND INCIDENCE OF RETINOPATHIES IN PREMATURE INFANTS. GÉRARD-LEFEBVRE, Pédiatrie **9**:823, 1954.

The author studied the influence of three "climates" upon prematures weighing less than 2000 gm.: (1) high temperature, humidity, and oxygen; (2) lower temperature, humidity, and oxygen (not exceeding 40%), and (3) same as (2) but no oxygen added to atmospheric air.

In his study of 200 prematures he found that, measured by the mortality rate, the slightly lower temperature (35-36 degrees) and relative hypoxia are well tolerated, in fact a somewhat better result was obtained by the second and third methods as compared to the first. With regard to the occurrence of retinopathies, the third method was definitely superior, in fact there were "no retinopathies for the last year, the period during which systematic oxygenation was discontinued."

Growth was somewhat retarded under the second and third methods until the infant abandoned his "spontaneous hibernation" and resumed normal growth.

GLASER, Baltimore.

THE EXPERIMENTAL "CONJUNCTIVITIS TOXOPLASMICA" OF THE RABBIT. SYLVIO ABREU FIALHO, Wien. klin. Wchnschr. **66**:817 (Oct. 22) 1954.

The conjunctiva of rabbits can hold virulent toxoplasma at least 21 days. It may be a possible portal of entrance. When toxoplasma is injected into the carotis primitiva an endogenous toxoplasma conjunctivitis can occur simultaneously with the uveitus. This happened in 4 animals out of 32 with intra-arterial toxoplasma injections. It was a conjunctivitis simplex with sparse secretion.

AMBERG, Rochester, Minn.

Cutaneous Diseases; Allergy

OFFICE MANAGEMENT OF ALLERGIC CHILDREN. MORTON ZALL, California Med. **82**:322 (April) 1955.

There is a high incidence of allergic disease in average pediatric practice. Proper diagnosis and treatment can and should be carried out by a higher percentage of practitioners. A thorough history is the most reliable diagnostic method. Skin testing is quite often a very necessary

diagnostic tool. Following testing, desensitization may be necessary. The technical details of these procedures should be common medical knowledge. Where desensitization is necessary and is properly carried out, the results are definitely better than with mere symptomatic management.

PRYOR, Redwood City, Calif.

DO YOU NEED TO KNOW ABOUT ALLERGY? J. HARVEY BLACK, Illinois M. J. **105**:5-10 (Jan.) 1954.

According to Black, everyone comes in contact with allergic conditions in one form or another and should be able to recognize them for what they are. Allergic conditions usually do not require hospitalization, consequently those whose work has been altogether in hospital wards see few allergic conditions and do not realize that in private practice they are frequent and important.

Allergic reaction can occur wherever there is vascular tissue, which means that all physicians will see allergic reactions and must consider them in the differential diagnoses of presumed organic diseases. Allergic conditions may be found in any part of the body, and they may closely mimic organic conditions.

Examples of conditions appearing in the various fields of practice which require consideration of allergy as the etiological factor are cited.

Allergy is a disease beginning in early life. At least two-thirds of clinical allergies develop before the age of 20 years. There are those who suffer from some sensitivity for awhile and then, without obvious explanation, lose it. But the far greater number continue to suffer until something is done about it.

After a long exposure to some food or contact substance, the patient may become sensitive to it. It is the patient, not the food or the environment, which has changed. Also, one does not become sensitive and develop symptoms from the first contact with the offending substance, but an incubation period is always required.

Most patients are only moderately or slightly sensitive to the antigen and, when other conditions are favorable, can tolerate the usual exposure without symptoms. Given the usual exposure and a simultaneous change in the weather, a cold, or an emotional upset and clinical symptoms are likely to follow. Thus we can accept the weather changes, colds, and emotional upsets as "accessory factors."

Multiple sensitivity is the rule. But people do not become allergic to great numbers of food. Patients are usually sensitive to a comparatively few things, and proper attention to these produce satisfactory relief. There are no infallible reactions in medicine, and skin tests are no exception to the rule. They must be only a part of the allergist's armamentarium.

BARBOUR, Peoria, Ill.

DIAGNOSIS AND TREATMENT OF PIGMENTED MOLES AND MELANOMAS. S. WILLIAM BECKER, Illinois M. J. **105**:113-118 (March) 1954.

Pigmented nevi may be (*a*) removed from sites of friction, and (*b*) treated for cosmetic reasons. A biopsy should be done on all specimens to eliminate melanoma.

A biopsy should be done on all pigmented lesions for the same reason. Melanoma is treated by radical surgery. Prognosis depends on early recognition of melanoma and institution of adequate surgical treatment.

FROM THE AUTHOR'S SUMMARY.

RESISTANT SUPERFICIAL FUNGOUS INFECTIONS. ALLAN L. LORINCZ, Illinois M. J. **105**:118-119 (March) 1954.

In this review of the superficial fungous infections, Lorincz points out that the recalcitrance of these infections is surprising. Clinically the hyperkeratotic element accompanying these infections is an important obstacle to therapy. Control of the lesions may require combinations of strong keratolytic or penetrating agents, such as salicylic acid on the skin or concentrated lithium bromide on the nails, as well as fungicides. Cure, especially in nail involvement, is practically impossible except on rare occasions by extremely persistent vigorous measures. Lesions on skin other than on palms and soles respond readily to ordinary antimycotic measures.

BARBOUR, Peoria, Ill.

DERMATITIS SEBORRHEIDES. SARA KOKIL, Ann. pædiat. **183**:32 (July) 1954.

The seborrheic dermatitis of the young infant is an illness of its own which bears no relationship with the allergic eczema of the infant or with seborrheic dermatitis of older children and adults. It is a winter disease, appearing every year from November till April, and is probably due to a lowering of the biotin content in breast milk and cows' milk during that season. The amounts of biotin thus become insufficient to guarantee normal keratinization of the epidermis. Biotin is a specific against seborrheic dermatitis. Oral or parenteral doses of 5 mg/day will cure seborrheic dermatitis in two to three weeks. Similar affections of older children are uninfluenced by biotin.

FROM THE AUTHOR'S SUMMARY.

A CASE OF DERMATOMYOSITIS TREATED SUCCESSFULLY WITH CORTISONE. G. BARTOLOZZI, Riv. clin. pediat. **53**:347 (April) 1954.

The author reports a 12-year-old child affected by acute dermatomyositis; a continuous cortisone treatment led to a complete and durable recovery.

FROM THE AUTHOR'S SUMMARY.

Miscellaneous

PROPHYLAXIS WITH CHEMOTHERAPEUTIC AND ANTIBIOTIC DRUGS. K. VON NITSCH, Deutsche Med. Wchnschr. **79**:1212 (Aug. 13) 1954.

The author reports observations in children. In 172 cases disease due to staphylococci, streptococci, and colibacillus infections occurred during usual sulfonamide treatment. In 62 cases such diseases occurred under penicillin treatment; the responsible organisms were penicillin-sensitive in vitro. Of 640 children, 46 acquired a febrile throat infection due to streptococci under prophylactic administration of 0.5 gm. sulfonamide three times a day, while among 710 children without such medication 68 such infections occurred. The difference is statistically insignificant. Adequate sulfonamide treatment of tonsillitis in 17 cases and with penicillin in 12 cases did not prevent an attack of acute rheumatic fever.

AMBERG, Rochester, Minn.

News and Comment

ANNOUNCEMENTS

Annual Congress of the Italian Society of Pediatrics.—The next annual Congress of the Italian Soicety of Pediatrics will be held in Perugia, on Oct. 9, 10, and 11, 1955. It will be organized by Prof. Pio Ritossa, Director of the Pediatric Clinic of the University of Perugia.

The subjects chosen by the Board of Directors are as follows:

1. Renal Dwarfisms: Prof. G. De Toni
2. Obesity in Infancy and Childhood: Prof. R. Pachioli
3. The Assistance to the Legitimate and Illegitimate Child in Our Legislature and in the World Legislature: Prof. C. Catteruccia, Prof. C. Garace, and Prof. E. Zambrano

Children's Exocrine Research Foundation.—A new foundation primarily devoted to the education and encouragement of research into the disease of pancreatic fibrosis has been announced by Dr. Paul Patterson, of Albany Medical College, Chairman of the Foundation's Medical Education Committee. Other officers are Dr. Wynne Sharples, Chairman of the Board of Trustees, and Dr. Sidney Farber, Chairman of the Scientific Advisory Board.

This foundation intends to have no public subscription of money, but to obtain grants from other foundations and interested givers and in turn to allocate the money to those research workers interested in doing investigation into the diseases of the exocrine system. Application for research grants can be made by communicating with the foundation's headquarters at 2300 Westmoreland St., Philadelphia.

Continuation Course in Pediatrics.—The University of Minnesota will present a continuation course in Pediatrics for Pediatricians next Sept. 21 and 22. Presented under the auspices of the Center for Continuation Study, the course will be held in the Mayo Memorial Auditorium on the University Campus. One-half day will be devoted to each of the following general subjects: infectious diseases, hypersensitivity diseases, central nervous system disorders, and endocrine and metabolic abnormalities.

The guest faculty will include Dr. Lewis Thomas, Professor of Pathology, New York University College of Medicine, New York City, who will also deliver the Irvine McQuarrie Lecture on Thursday evening, Sept. 22. The course will be presented under the direction of Dr. John A. Anderson, Head, Department of Pediatrics. Registrants will also be invited to attend the meeting of the Northwestern Pediatric Society, which will be held on Friday, Sept. 23.

Lodging and meal accommodations are available at the Center for Continuation Study.

VIII International Congress of Paediatrics.—The VIII International Congress of Paediatrics will be held in Copenhagen, on July 22-27, 1956.

The Scientific program comprises plenary sessions, round-table conferences, sectional meetings, and an exhibition.

At the plenary sessions the following lectures will be held:

Monday, July 23

I. Prenatal Injuries and Malformations.
   1. Genetic injuries from irradiation (atomic bomb).
   2. Prenatal infections.
   3. Prenatal prophylaxis.

II. Chemical Agents.
   1. Fluoridated water in the prevention of dental caries.
   2. Dangers involved in the use of antibiotics.
   3. Dangers from industrially manufactured foods.

Tuesday, July 24

I. Pathology of the Newborn: Anoxia.
   1. Mechanism of anoxia.
   2. Pathological anatomy of anoxia.
   3. Oxygen therapy—value and risks.

II. Surgery.
   1. Malignant diseases in childhood.
   2. Urological problems.
   3. Late results of operation for cyanotic heart diseases.

Wednesday, July 25

I. Child Psychiatry.
   1. Neuroses in childhood.
   2. Prevention of accidents.
   3. Early diagnosis of mental deficiency.

II. Neurology.
   1. Hydrocephalus.
   2. Cerebral palsy—results of long-term physiotherapy.
   3. Kernicterus.

Thursday, July 26

I. Infections.
   1. Vaccination against poliomyelitis.

II. Allergy.
   1. Bacterial allergy: Diagnosis and incidence.
   2. Bacterial allergy: Treatment and results.

Friday, July 27

I. Problems in Tropical Pediatrics.
   1. Kwashiorkor.
   2. Chagas' Disease.
   3. Ascariasis.

II. Tuberculosis.
   1. Prophylaxis of tuberculosis.
   2. Treatment of primary tuberculosis.
   3. Treatment of tuberculous meningitis.

Proffered papers will be read in sectional meetings.

It is also planned to arrange round-table conferences with the following subjects:

1. Auricular septal defect.
2. Epilepsy.
3. Leukemia.
4. Hemophilia.
5. Amino acid metabolism.
6. Nephrosis.
7. Water and electrolyte metabolism in dehydration.
8. The adrenogenital syndrome.

Films of pediatric interest will be shown in the Congress Cinema.

A scientific and technical exhibition will be arranged in connection with the Congress.

The preliminary program will be sent out in a few weeks.

For further information please apply to: VIII International Congress of Paediatrics, Domus Medica, 12 A Kristianiagade, Copenhagen Ø, Denmark.

Books

Fisiología y patología de la alimentación del lactante. By L. F. Meyer and E. Nassau. Price, not given. Pp. 499, with 61 illustrations. Assandri, Cordoba, Argentina, 1954.

Die Bedeutung der Frühkindlichen Hirnschädigung für die Kinderpsychiatrie. By Gerhard Gollnitz. Price, 19.50 Deutsche marks. Pp. 149, with 76 illustrations. VEB Georg Thieme, Hainstrasse 17-19, Leipzig C1, 1954.

Developpement psycho-moteur du premier age. By Cyrille Koupernik. Price, 500 francs. Pp. 197, with 57 illustrations. Presses universitaires de France, 108 boulevard Saint-Germain, Paris, 6e, 1954.

Culture and Human Fertility: A Study of the Relation of Cultural Conditions to Fertility in Non-Industrial and Transitional Societies. By Frank Lorimer, with special contributions by Meyer Fortes, K. A. Busia, Audrey I. Richards, Priscilla Reining, and Giorgio Mortara. Price, $4.50. Pp. 513. UNESCO, Columbia University Press, 2960 Broadway, New York 27, 1955.

Health Supervision of Young Children: A Guide for Practicing Physicians and Child Health Conference Personnel. By Committee on Child Health of the American Public Health Association. Price, $2. Pp. 180. American Public Health Association, 1790 Broadway, New York 19, 1955.

Notes on Infant Feeding. Edition 4. By Stanley Graham and Robert A. Shanks. Price, $2. Pp. 74, with no illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2, 1954.

This paper-bound booklet is an outline of infant feeding for use by the medical students at the Royal Hospital for Sick Children, Glasgow, Scotland.

The principles stressed are the same as those used in the United States. The methods used in artificial feeding of infants are based on the caloric requirements of the infant and the caloric values of the foods used.

The fundamental physiological principles of feeding are briefly surveyed.

While the outline is brief, it is complete, and no space is wasted on discussions unrelated to the subject.

It is interesting to note that the British government supplies orange juice concentrate for vitamin C, fortified cod liver oil for vitamin D, and powdered milk to infants without charge.

The booklet makes infant feeding a simplified subject, which is as it should be currently.

Textbook of Pediatrics. Edited by Waldo E. Nelson. Price, $15.00. Pp. 1581, with 440 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia, 1954.

This edition is the third under the editorship of Dr. Nelson. It follows the fifth edition by four years and is the first edition on which the name of Mitchell is missing. Previous editions of this book were widely accepted as leaders in the field of Pediatrics. The recent edition lives up to this reputation in every respect. It has been extensively rewritten. How wide the revision has been is partially indicated by the fact that 12 contributors to the fifth edition are missing in this one, while 19 new authors have been added. Thus there are 19 entirely new sections, while practically all of the others have been revised.

Some of the chapters are reorganized. The discussions of the newborn and the premature infant are combined in a single chapter instead of two. Malignant tumors and miscellaneous diseases have been moved to a more logical location toward the end of the book. Virus infections are more completely covered. New chapters on burns and radiation injury are added.

In spite of extensive revision it is startling to note that instead of the usual trend toward larger and larger texts, this one has been reduced in size by 100 pages. There is no apparent loss in comprehensive coverage. The index, despite the reduction in text has been expanded by 25 pages.

Without question, this edition will be as well received as were its predecessors.

Handbook of Cardiology for Nurses. By Walter Modell, M.D., and Doris R. Schwartz, M.D. Price, $4.25. Pp. 320, with 3 illustrations. Springer Publishing Company, 44 E. 23d St., New York, 1954.

This handbook follows the usual pattern of textbooks for nurses. The symptoms and signs of the usual types of heart disease are described, followed by a discussion of the various forms of treatment, including drugs, surgery, diet, climate, and psychotherapy. The discussion is clear and orderly. The book can be heartily recommended to the nurse who is devoting herself to the care of cardiac patients.

Case Studies in Childhood Emotional Disabilities. Vol. 1. Edited by George E. Gardner, Ph.D., M.D. Price, $5. Pp. 368. American Orthopsychiatric Association, Inc., New York, 1953.

Since 1950, the annual meetings of the American Orthopsychiatric Association have taken the form of a series of workshops where case studies are presented to relatively small groups of professionally trained people. This volume is a collection of 13 such case presentations by groups of psychiatrists and psychoanalysts from various clinics. Each report consists of detailed psychiatric interviews with the child and frequently with the mother. The reports are an example of good teamwork between psychiatrist, social worker, and clinic group.

The cases include age groups ranging from early childhood to adolescence. The emotional disabilities studied were stuttering, petit mal with enuresis, delinquent adolescence, acute anxiety, destructive behavior, and obesity.

One case presentation, entitled "Psychogenic Diarrhea and Phobia in a 6½ Year Old Girl," by Melitta Sperling, gives a detailed report of a child whose diarrhea began in infancy and persisted several years. The author makes no mention of common physical causes for the diarrhea, but assumes without discussion or proof that the diarrhea is psychogenic due to phobia.

The case studies are for the most part psychoanalytic in their approach, which makes this collection of presentation a valuable contribution to teaching in the field of psychoanalysis. To the pediatrician, the book is a reminder that severely emotionally disturbed children require help from well-trained psychiatric teams.

The Voice of Neurosis. By Paul J. Moses, M.D. Price, $4. Pp. 125. Grune & Stratton, Inc., 381 4th Ave., New York, 1954.

The relationship between vocal abnormalities and emotional disturbances has been recognized for many years. But, as the author of this particular work points out in his introduction, the training of the psychiatrist does not include analysis of the voice, nor does the training of the laryngologist provide sufficient background for his understanding of emotional problems. Since Dr. Moses represents one of the rare individuals whose qualifications apparently include considerable experience in both fields, this monograph warrants careful study.

A plea is made for the development of acoustic examination of the human voice as a scientific process. This ability to perceive the human voice correctly and to interpret it properly is spoken of as "creative hearing." Among other chapters of this work are those on the ontogenesis of the voice, on acoustic dimensions of voice (respiration, range, registers, resonance, and rhythm), other dimensions (melody, intensity, speed, accents, emphasis) and further significant features of voice, such as pathos, mannerisms, melism (personal appeal), and exactness. In the final chapters are to be found excellent discussions of the vocal features of neurosis, illustrated with applicable case histories.

By and large this work must be regarded as a highly specialized monograph. Laryngologists, psychiatrists, and speech therapists will be stimulated by the unified approach to their common problems.

La Terapia della nefrosi nel bambino. By Carlo Imperato. Price, 1500 lire. Pp. 245. Edizioni scientifiche italiane, Galleria Umberto I, 83, Naples, 1954.

"The treatment of the nephrosis syndrome is always a field of therapy in which the intelligence, the experience and the tenacity of the physician are found of the greatest use." Thus Imperato concludes this treatise on nephrosis with especial emphasis on its treatment.

Twelve cases of nephrosis in children 2 to 12 years of age are presented in detail; each child has been the subject of prolonged hospital study; many therapeutic procedures were tried. Including three more recent cases, he is able to report clinical cures in nine, improvement in five, and no change in one. The urinary findings and electrophoresis tests on the sera of seven of these nine were also normal. In these seven, the duration of the cure was at the time of the writing from 9 to 26 months.

The overcoming of the hypoproteinemia is regarded as the primary function of his recommended therapy. A high-protein diet and frequent intravenous injections of blood serum and of amino acids are also means of obtaining this result. The second aim in therapy is the limitation of salt intake. The third aim is the giving of corticotropin (ACTH) and cortisone; these hormones were found to be very effective in overcoming the edema. The dosage, the number of cycles, and the duration of this treatment had to be adjusted to the individual case. The effect was frequently only transitory, but in the writer's experience, these hormones were the most effective measures in restoring normal proteinemia and cholesterolemia values in nephrosis patients. The fourth aim in treating nephrosis is the use of antibiotics in preventing and relieving intercurrent infections.

Kinderorthopädie. By Rupprecht Bembeck. Price, not given. Pp. 226, with 174 illustrations. Georg Thieme Verlag, Stuttgart, Herdweg 63, 1954.

This volume is devoted exclusively to children's orthopedics and reflects the current thinking in Germany about the deformities, their prevention and correction.

Congenital clubfoot and dislocated hip are emphasized. The author has carefully selected his illustration material to emphasize the important concepts of pathogenesis, radiology, and clinical findings in these conditions.

The orthopedic problems of the child with poliomyelitis and the cerebral spastic are not emphasized.

The author emphasizes only those fractures which produce deformity.

The treatment of the various conditions is not given in detail, but the principles of treatment for each condition are ably stated. It is a pleasure to recommend highly this German textbook of children's orthopedics to the readers of this JOURNAL.

Die Lunge des Kindes. By Prof. Dr. Stefan Engel. Price, 29.70 marks. Pp. 286, with 283 illustrations. Georg Thieme Verlag, Stuttgart, Herdweg 63, 1950.

The author is well known for his many publications on the respiratory system in childhood. The present volume deals with the growth, anatomy, physiology, and pathology of the lungs in different age periods, from newborn period through puberty. The largest part of the book is devoted to the anatomy and histology of the lungs and the bronchial tree, while the physiology gets less attention. The author justifies his anatomical approach as follows: "I am conscious that my approach is contrary to the present tendency. Anatomy is old-fashioned, function is modern. But where do we go, when we withdraw more and more from the solid anatomical foundations?"

Engel's book is based almost entirely on his own investigations. Outstanding are the chapters on the pathology of the bronchial glands and the various types of pneumonia. Very stimulating is the concept of age disposition. Engel's work provides a solid anatomical basis for the study and understanding of the respiratory diseases in childhood. Paper, print, and illustrations are excellent.

Reducing Emotion Trauma in Hospitalized Children. By O. A. Faust, M.D., M. M. Burtt, M.D., E. G. Cermak, M.D., K. Jackson, M.D., and R. Winkley, A.B. Price, not given. Albany Research Project, Albany, N. Y., 1952.

This is a three-year study of 140 tonsillectomized children forming the basis of a study in psychosomatic pediatrics. This research project originated from the departments of pediatrics and anesthesiology of the Albany Medical College. The hospital-anesthesia-operation experience

of tonsillectomy in young children is considered from the standpoint of emotional trauma in an attempt to develop a technique to reduce it. A "study" group and a "control" group were studied by a selected staff, and the age limits were 5 to 7 years, inclusive. Each child was visited in the home one week prior to hospitalization by a psychiatric social worker and the preoperative evening by the selected staff anesthesiologist. The child was made fully aware of the events related to anesthesia. The spirit of friendliness, warmth, and happiness in the hospital ward was stressed. Unnecessary preoperative procedures were eliminated.

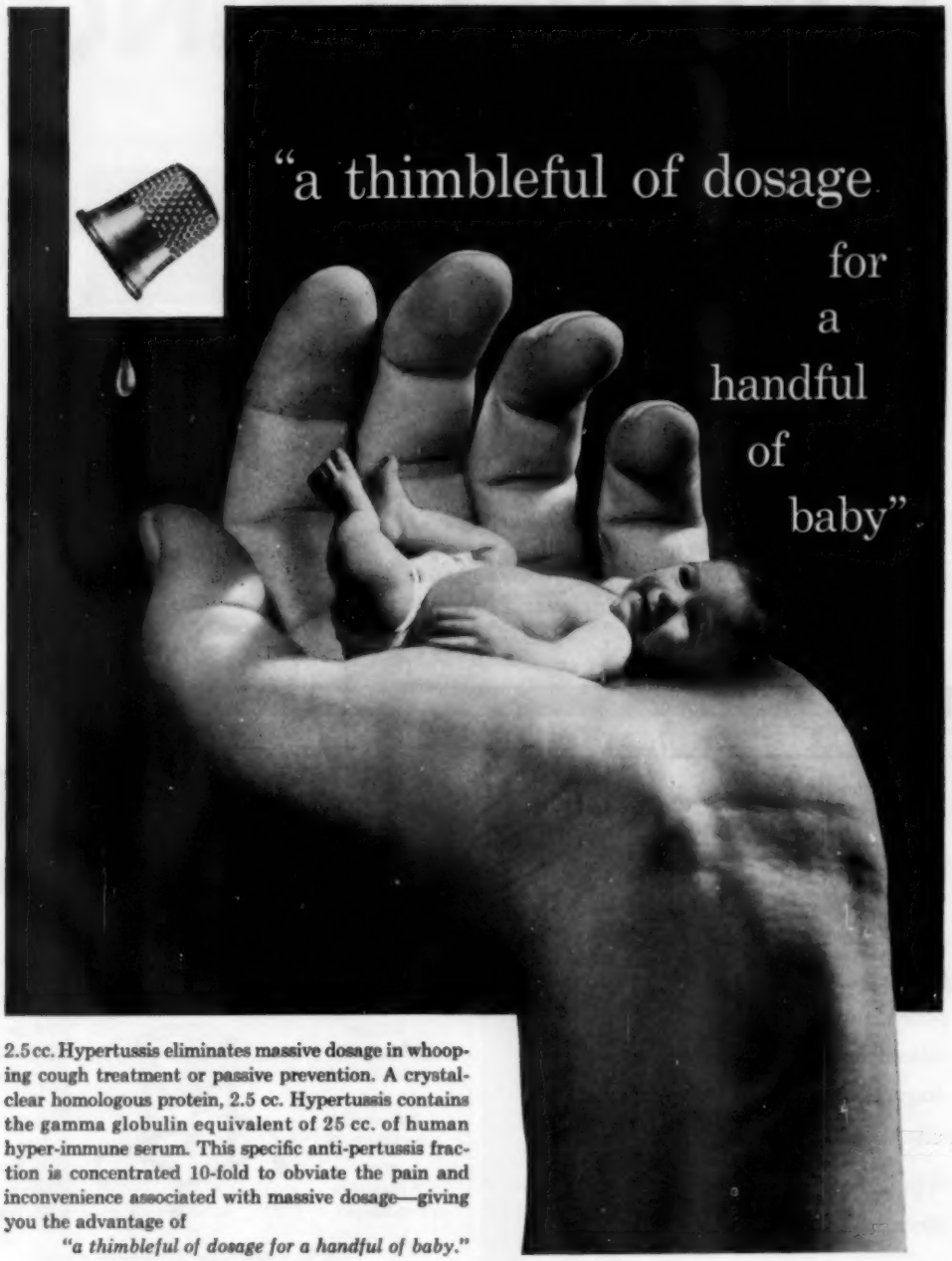
The case worker must be trained in the art of interviewing and experienced in work with children. Translating data into terms capable of codification requires experience with the behavior and emotional reactions of children.

One portion of the cases had sedative premedication, secobarbital (Seconal) or pentobarbital (Nembutal), ¾ grain two hours before operation. The other portion psychologically prepared had neither the undesirable side-effects of stormy inductions nor of heavy premedication. When sedative and psychological preparation were used together, induction time was increased. A properly prepared child, rather than experiencing emotional trauma, may in some instances strengthen his courage and self assurance. Thirty cases of psychologically well-prepared children proved that less anesthetic agent was used, induction was more quiet, there was a milder excitement stage, and there was a more quiet operating room and a lack of physiologic depression from premedication. The patient learns to approach new situations with trust and confidence that doctors and nurses will treat him fairly, that the procedure is necessary and not punitive. Whether the parent should stay with the child postoperatively depends on the parent's stability. A child well adjusted to a family environment of love, trust, and security requires and deserves factual preparation, and the time of hospitalization should preferably suit his own emotional balance.

Emotional trauma is considered to be associated with an increase in any of the negative feelings: anxiety, suspiciousness, resentment, hostility, inadequacy, insecurity, or a desire to retaliate. Such a psychologic trauma may be exhibited in appetite and eating habits, dependency, disposition, sleep habits, and mannnerisms.

The pediatrician is in the key position to dispel many preoperative anxieties. The result will depend on the pediatrician, the child, and all hospital contacts.

This reviewer feels that this report contains unnecessary detail, but opinion will vary according to the basic interests of the reader. Surgeons will welcome such a study as highly important and the psychologic preparation as far superior to the sedation, except in unusual circumstances.



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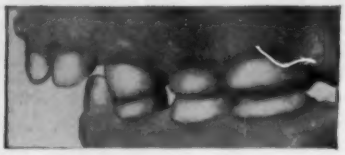

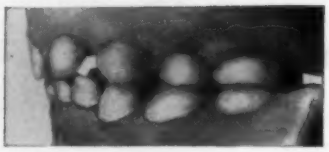

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(1) Jeans, P. C., in A. M. A. Handbook of Nutrition, ed. 2, Philadelphia, Blakiston, 1951, pp. 275-278.

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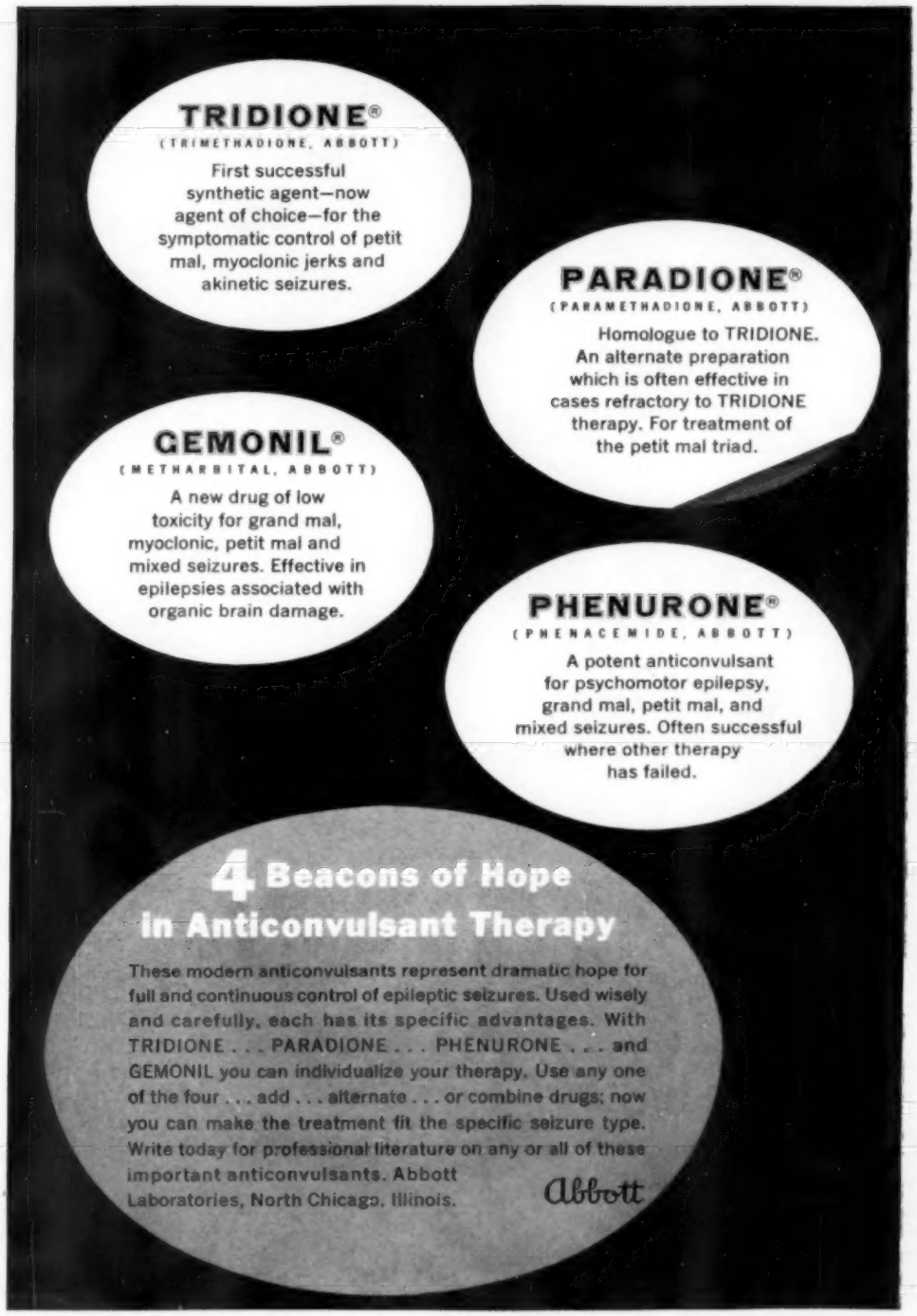
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